

**WEST**

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Search Results - Record(s) 1 through 7 of 7 returned.

☐ 1. Document ID: US 6072047 A

L1: Entry 1 of 7

File: USPT

Jun 6, 2000

US-PAT-NO: 6072047

DOCUMENT-IDENTIFIER: US 6072047 A

TITLE: Receptor that binds trail

DATE-ISSUED: June 6, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP	CODE	COUNTRY
Rauch; Charles	Bainbridge Island	WA	N/A		N/A
Walczak; Henning	Seattle	WA	N/A		N/A

US-CL-CURRENT: 536/23.5; 435/252.3, 435/320.1, 435/325, 435/6,  
435/69.1, 530/350, 536/24.3

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 2. Document ID: WO 9903992 A1

L1: Entry 2 of 7

File: EPAB

Jan 28, 1999

PUB-NO: WO009903992A1

DOCUMENT-IDENTIFIER: WO 9903992 A1

TITLE: TRAIL RECEPTOR

PUBN-DATE: January 28, 1999

## INVENTOR-INFORMATION:

NAME	COUNTRY
DEGLI-ESPOSTI, MARIAPIA	N/A

INT-CL (IPC): C12N 15/12; C12N 15/62; C07K 14/715; C07K 16/28;  
C07K 16/46; A61K 38/17

EUR-CL (EPC): C07K014/705

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 3. Document ID: WO 9835986 A1

L1: Entry 3 of 7

File: EPAB

Aug 20, 1998

PUB-NO: WO009835986A1

DOCUMENT-IDENTIFIER: WO 9835986 A1

TITLE: RECEPTOR THAT BINDS TRAIL

PUBN-DATE: August 20, 1998

## INVENTOR-INFORMATION:

NAME

COUNTRY

RAUCH, CHARLES

N/A

WALCZAK, HENNING

N/A

INT-CL (IPC): C07K 14/435; C07K 14/715; C07K 16/28; C12N 15/12;  
C12N 15/19

EUR-CL (EPC): C07K014/705; C07K014/715

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 4. Document ID: EP 1012179 A2, WO 9912963 A2, AU 9893863 A

L1: Entry 4 of 7

File: DWPI

Jun 28, 2000

DERWENT-ACC-NO: 1999-276942

DERWENT-WEEK: 200035

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TITLE: Novel tumor necrosis factor receptor proteins TRAIL-R2  
and TRAIL-R3

INVENTOR: TSCHOPP, J

PRIORITY-DATA: 1998US-0084422 (May 6, 1998), 1997US-0058631  
(September 12, 1997)

## PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1012179 A2	June 28, 2000	E	000	C07K014/00
WO 9912963 A2	March 18, 1999	E	028	C07K014/00
AU 9893863 A	March 29, 1999	N/A	000	C07K014/00

INT-CL (IPC): C07K 14/00

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 5. Document ID: EP 998561 A1, WO 9903992 A1, AU 9883957 A

L1: Entry 5 of 7

File: DWPI

May 10, 2000

DERWENT-ACC-NO: 1999-132236

DERWENT-WEEK: 200027

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TITLE: New isolated TRAIL receptor polypeptides - used to develop products for treating e.g. thrombotic microangiopathy, multiple sclerosis, systemic lupus erythematosus or HIV infection

INVENTOR: DEGLI-ESPOSTI, M

PRIORITY-DATA: 1997US-0892119 (July 15, 1997)

## PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 998561 A1	May 10, 2000	E	000	C12N015/12
WO 9903992 A1	January 28, 1999	E	050	C12N015/12
AU 9883957 A	February 10, 1999	N/A	000	C12N015/12

INT-CL (IPC): A61K 38/17; C07K 14/715; C07K 16/28; C07K 16/46; C12N 15/12; C12N 15/62

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 6. Document ID: MX 9907234 A1, WO 9835986 A1, AU 9866505 A, EP 1005488 A1, US 6072047 A, NZ 336929 A

L1: Entry 6 of 7

File: DWPI

Jan 1, 2000

DERWENT-ACC-NO: 1998-480767  
DERWENT-WEEK: 200115  
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TITLE: New TRAIL receptor protein and related oligomers,  
nucleic acid, vectors - used to inhibit TRAIL activity, e.g. in  
cases of thrombocytic purpura, clotting in small blood vessels  
etc., also for diagnosis

INVENTOR: RAUCH, C; WALCZAK, H

PRIORITY-DATA: 1997US-0883036 (June 26, 1997), 1997US-0799861  
(February 13, 1997), 1997US-0815255 (March 12, 1997),  
1997US-0829536 (March 28, 1997), 1997US-0869852 (June 4, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
MX 9907234 A1	January 1, 2000	N/A	000	C07K014/435
WO 9835986 A1	August 20, 1998	E	056	C07K014/435
AU 9866505 A	September 8, 1998	N/A	000	C07K014/435
EP 1005488 A1	June 7, 2000	E	000	C07K014/435
US 6072047 A	June 6, 2000	N/A	000	C07H021/04
NZ 336929 A	November 24, 2000	N/A	000	C07K016/28

INT-CL (IPC): C07H 21/04; C07K 14/435; C07K 14/715; C07K 16/28;  
C12N 15/12; C12N 15/19; C12N 15/63

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWC	Draw Desc	Image
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☐ 7. Document ID: JP 2001505060 W, WO 9830693 A2, AU 9862386 A, EP 990031  
A2, CN 1247567 A

L1: Entry 7 of 7

File: DWPI

Apr 17, 2001

DERWENT-ACC-NO: 1998-399141  
DERWENT-WEEK: 200128  
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Human TRAIL receptor without an intracellular domain  
polypeptide - used in the diagnosis of immune system-related  
disorder(s)

INVENTOR: EBNER, R; FENG, P ; GENTZ, R L ; NI, J ; RUBEN, S M ;  
WEI, Y ; YU, G

PRIORITY-DATA: 1997US-0054885 (August 7, 1997), 1997US-0035496  
(January 14, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2001505060 W	April 17, 2001	N/A	150	C12N015/09
WO 9830693 A2	July 16, 1998	E	091	C12N015/12
AU 9862386 A	August 3, 1998	N/A	000	C12N015/12
EP 990031 A2	April 5, 2000	E	000	C12N015/12
CN 1247567 A	March 15, 2000	N/A	000	C12N015/12

INT-CL (IPC): A61K 38/00; A61K 38/17; A61K 39/395; A61K 45/00;  
A61P 1/16; A61P 7/00; A61P 9/10; A61P 19/08; A61P 25/16; A61P  
25/28; A61P 31/12; A61P 35/00; A61P 37/00; A61P 37/06; A61P  
43/00; C07K 14/705; C07K 14/715; C07K 16/28; C12N 1/21; C12N  
5/10; C12N 15/09; C12N 15/12; C12N 15/63; C12N 15/70; C12N  
15/85; C12N 15/86; C12P 21/02; C12P 21/08

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWC	Draw Desc	Image
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Term	Documents
TNF-RELATED.DWPI,EPAB,JPAB,USPT,PGPB.	49
TNF-RELATEDS	0
APOPTOSIS-INDUCING.DWPI,EPAB,JPAB,USPT,PGPB.	220
APOPTOSIS-INDUCINGS	0
LIGAND.DWPI,EPAB,JPAB,USPT,PGPB.	53049
LIGANDS.DWPI,EPAB,JPAB,USPT,PGPB.	35310
RECEPTOR.DWPI,EPAB,JPAB,USPT,PGPB.	84644
RECEPTORS.DWPI,EPAB,JPAB,USPT,PGPB.	44971
TRAIL-R.DWPI,EPAB,JPAB,USPT,PGPB.	6
TRAIL-RS	0
((TNF-RELATED ADJ APOPTOSIS-INDUCING ADJ LIGAND ADJ RECEPTOR) OR TRAIL-R).USPT,PGPB,JPAB,EPAB,DWPI.	7

US Patents Full-Text Database  
US Pre-Grant Publication Full-Text Database  
JPO Abstracts Database  
EPO Abstracts Database  
Derwent World Patents Index

Database: IBM Technical Disclosure Bulletins

Refine Search:

TNF-related apoptosis-inducing ligand  
receptor or TRAIL-r[Clear](#)**Search History**

Today's Date: 7/1/2001

Term	Documents
TNF-RELATED.DWPI,EPAB,JPAB,USPT,PGPB.	49
TNF-RELATEDS	0
APOPTOSIS-INDUCING.DWPI,EPAB,JPAB,USPT,PGPB.	220
APOPTOSIS-INDUCINGS	0
LIGAND.DWPI,EPAB,JPAB,USPT,PGPB.	53049
LIGANDS.DWPI,EPAB,JPAB,USPT,PGPB.	35310
RECEPTOR.DWPI,EPAB,JPAB,USPT,PGPB.	84644
RECEPTORS.DWPI,EPAB,JPAB,USPT,PGPB.	44971
TRAIL-R.DWPI,EPAB,JPAB,USPT,PGPB.	6
TRAIL-RS	0
(TNF-RELATED APOPTOSIS-INDUCING LIGAND RECEPTOR OR TRAIL-R ).USPT,PGPB,JPAB,EPAB,DWPI.	7

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Documents, starting with Document:

7

**Display Format:** CIT

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<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
USPT,PGPB,JPAB,EPAB,DWPI	TNF-related apoptosis-inducing ligand receptor or TRAIL-r	7	<u>L1</u>

C



\*\*\*\*\*STN Columbus\*\*\*\*\*  
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FILE 'MEDLINE'  
FILE 'JAPIC'  
FILE 'BIOSIS'  
FILE 'SCISEARCH'  
FILE 'WPIDS'  
FILE 'CAPLUS'  
FILE 'EMBASE'  
=> s TNF-related apoptosis-inducing ligand receptor# or TRAIL-  
TRAIL-  
5 FILES SEARCHED...

L1 83 TNF-RELATED APOPTOSIS-INDUCING  
LIGAND RECEPTOR# OR TRAIL-R

=> dup rem 11

PROCESSING COMPLETED FOR L1  
L2 41 DUP REM L1 (42 DUPLICATES REMOVED)

=> d 12 ibib arts 1-41

'ANS' IS NOT A VALID FORMAT  
In a multifile environment, a format can only be used if it is  
valid  
in at least one of the files. Refer to file specific help messages  
or the STNGUIDE file for information on formats available in  
individual files.  
REENTER DISPLAY FORMAT FOR ALL FILES  
(FILEDEFAULT):end

=> d 12 ibib abs 1-41

L2 ANSWER 1 OF 41 MEDLINE  
DUPLICATE 1  
ACCESSION NUMBER: 2001292864 MEDLINE  
DOCUMENT NUMBER: 21238332 PubMed ID: 11278665  
TITLE: MAPK/ERK overrides the apoptotic signaling  
from Fas, TNF,  
and TRAIL receptors.

AUTHOR: Tran S E; Holmstrom T H; Ahonen M;  
Kahani V M; Eriksson J E  
CORPORATE SOURCE: Turku Centre for Biotechnology,  
POB 123, FIN-20521,  
University of Turku, Turku, Finland.

SOURCE: JOURNAL OF BIOLOGICAL  
CHEMISTRY, (2001 May 11) 276 (19)  
16484-90.  
Journal code: HIV; 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200106  
ENTRY DATE: Entered STN: 20010618  
Last Updated on STN: 20010618  
Entered PubMed: 20010507  
Entered Medline: 20010614

AB The tumor necrosis factor (TNF), Fas, and TNF-related  
apoptosis-inducing  
ligand (TRAIL) receptors (R) are highly specific  
physiological mediators  
of apoptotic signaling. We observed earlier that a number of  
FasR-insensitive cell lines could redirect the proapoptotic  
signal to an  
anti-apoptotic ERK1/2 signal resulting in inhibition of  
caspase  
activation. Here we determine that similar mechanisms are  
operational in  
regulating the apoptotic signaling of other death receptors.  
Activation of  
the FasR, TNF-R1, and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* ,  
respectively, rapidly  
induced subsequent ERK1/2 activation, an event  
independent from caspase  
activity. Whereas inhibition of the death receptor-mediated  
ERK1/2  
activation was sufficient to sensitize the cells to apoptotic  
signaling  
from FasR and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* , cells were  
still protected from  
apoptotic TNF-R1 signaling. The latter seemed to be due to  
the strong  
activation of the anti-apoptotic factor NF-kappaB, which  
remained inactive  
in FasR or \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* signaling.  
However, when the cells  
were sensitized with cycloheximide, which is sufficient to  
sensitize the  
cells also to apoptosis by TNF-R1 stimulation, we noticed  
that  
adenovirus-mediated expression of constitutively active  
MKK1 could rescue  
the cells from apoptosis induced by the respective receptors

by preventing  
caspase-8 activation. Taken together, our results show that  
ERK1/2 has a  
dominant protecting effect over apoptotic signaling from the  
death  
receptors. This protection, which is independent of newly  
synthesized  
proteins, acts in all cases by suppressing activation of the  
caspase  
effector machinery.

L2 ANSWER 2 OF 41 SCISEARCH COPYRIGHT 2001 ISI  
(R)  
ACCESSION NUMBER: 2001:316522 SCISEARCH  
THE GENUINE ARTICLE: 420QT  
TITLE: Relative resistance of fresh isolates of  
melanoma to tumor  
necrosis factor-related apoptosis-inducing ligand  
(TRAIL)-induced apoptosis

AUTHOR: Nguyen T; Zhang X D; Hersey P (Reprint)  
CORPORATE SOURCE: Immunol & Oncol Unit, Room  
443, David Maddison Clin Sci  
Bldg, Corner King, Newcastle, NSW 2300,  
Australia

(Reprint); Newcastle Mater Hosp, Immunol &  
Oncol Unit,  
Newcastle, NSW 2300, Australia

COUNTRY OF AUTHOR: Australia  
SOURCE: CLINICAL CANCER RESEARCH, (MAR  
2001) Vol. 7, No. 3, Supp.  
[S], pp. 966S-973S.

Publisher: AMER ASSOC CANCER

RESEARCH, PO BOX 11806,  
BIRMINGHAM, AL 35202 USA.  
ISSN: 1078-0432.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 27

\*ABSTRACT IS AVAILABLE IN THE ALL

AND IALL FORMATS\*

AB In previous studies, we have shown that tumor necrosis  
factor-related  
apoptosis-inducing ligand (TRAIL) could induce varying  
degrees of  
apoptosis in approximately two-thirds of human melanoma  
lines. In the  
present study, we have examined the sensitivity of fresh  
isolates and  
early passages of melanoma cells to TRAIL-induced  
apoptosis from eight  
patients. We found that fresh isolates were relatively  
resistant to  
TRAIL-induced apoptosis and that this appeared to be  
associated with low  
TRAIL death receptor ( \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* )  
expression.

\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* expression was also  
undetectable in tissue  
sections from the same melanoma. We attempted to create a  
model for these  
findings by generation of TRAIL-resistant melanoma lines  
from  
TRAIL-sensitive lines grown for prolonged periods in  
TRAIL. The resulting  
TRAIL-resistant melanoma cell lines had low  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*  
expression, and sensitivity to TRAIL was increased-rapidly  
by pretreatment  
with proteasome inhibitors known to inhibit activation of  
nuclear  
factor-kappaB. However, the latter treatment had no  
significant effect on  
the sensitivity of fresh isolates to TRAIL. The levels of the  
inhibitors  
of apoptosis, Flice-like inhibitory protein and Bcl-2, also did  
not relate  
to resistance to TRAIL-induced apoptosis. These results  
suggest that  
down-regulation of \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* on  
melanoma cells may be  
the primary determinant of resistance of fresh isolates to  
TRAIL, and the  
basis for this requires further investigation.

L2 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2001:311743 CAPLUS  
TITLE: Relative resistance of fresh isolates of  
melanoma to  
tumor necrosis factor-related  
apoptosis-inducing  
ligand (TRAIL)-induced apoptosis  
AUTHOR(S): Nguyen, Tam; Zhang, Xu Dong;  
Hersey, Peter  
CORPORATE SOURCE: Oncology and Immunology  
Unit, Newcastle Mater  
Hospital, Newcastle, 2300, Australia  
SOURCE: Clin. Cancer Res. (2001), 7(3, Suppl.),  
966S-973S  
CODEN: CCREF4; ISSN: 1078-0432  
PUBLISHER: American Association for Cancer

Research  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB In previous studies, we have shown that tumor necrosis  
factor-related  
apoptosis-inducing ligand (TRAIL) could induce varying  
degrees of  
apoptosis in approx. two-thirds of human melanoma lines.  
In the present  
study, we have examd. the sensitivity of fresh isolates and  
early passages  
of melanoma cells to TRAIL-induced apoptosis from eight  
patients. We  
found that fresh isolates were relatively resistant to  
TRAIL-induced  
apoptosis and that this appeared to be assocd. with low  
TRAIL death  
receptor ( \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* ) expression.  
\*\*\*TRAIL\*\*\*  
\*\*\*R\*\*\* expression was also undetectable in tissue  
sections from the  
same melanoma. We attempted to create a model for these  
findings by  
generation of TRAIL-resistant melanoma lines from  
TRAIL-sensitive lines  
grown for prolonged periods in TRAIL. The resulting  
TRAIL-resistant  
melanoma cell lines had low \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*  
expression, and  
sensitivity to TRAIL was increased rapidly by pretreatment  
with proteasome  
inhibitors known to inhibit activation of nuclear  
factor-kappaB.

However, the latter treatment had no significant effect on  
the sensitivity  
of fresh isolates to TRAIL. The levels of the inhibitors of  
apoptosis,  
Flice-like inhibitory protein and Bcl-2, also did not relate to  
resistance  
to TRAIL-induced apoptosis. These results suggest that  
down-regulation of  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* on melanoma cells may be  
the primary determinant  
of resistance of fresh isolates to TRAIL, and the basis for  
this requires  
further investigation.

REFERENCE COUNT: 27  
REFERENCE(S): (1) Ashkenazi, A; J Clin Investig  
1999, V104, P155

CAPLUS  
(3) Emery, J; J Biol Chem 1998, V273, P14363

CAPLUS  
(5) Griffith, T; Curr Opin Immunol 1998, V10,  
P599

CAPLUS  
(6) Griffith, T; J Immunol 1998, V161, P2833

CAPLUS  
(7) Griffith, T; J Immunol 1999, V162, P2597

CAPLUS  
ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L2 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2001:443506 CAPLUS

TITLE: Progress in study of TRAIL and  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\*

AUTHOR(S): Fan, Qinglin; Song, Lihua  
CORPORATE SOURCE: The Biological Institute of Anhui  
Province, Hefei,  
230031, Peop. Rep. China

SOURCE: Zhongguo Shenghua Yaowu Zazhi  
(2001), 22(2), 103-105  
CODEN: ZSYZFP; ISSN: 1005-1678

PUBLISHER: Zhongguo Shenghua Yaowu Zazhi  
Bianjibu

DOCUMENT TYPE: Journal; General Review

LANGUAGE: Chinese

AB A review with 16 refs. on progress in study of TRAIL and  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* with subdivision headings: (1) the discovery of  
TNF related  
apoptosis-inducing ligand (TRAIL) and its receptor (

\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* ); (2) the mol. mechanism of TRAIL action and  
(3) the forecast of  
its application.

L2 ANSWER 5 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2001:287244 BIOSIS

DOCUMENT NUMBER: PREV200100287244  
TITLE: Death receptors in microvascular endothelial  
cells.

AUTHOR(S): Esser, P. J. (1); Luther, T. T. (1);  
Schermeyer, U. (1);  
Kociok, N. (1); Esser, J. M. (1); Krott, R. (1);  
Brunner,

R. (1); Kirchhof, B. (1); Joussen, A. M. (1)  
CORPORATE SOURCE: (1) Dept. of Ophthalmology,  
University Eye Clinic Cologne,

Cologne Germany  
SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S89. print  
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 6 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2001:70865 BIOSIS  
DOCUMENT NUMBER: PREV200100070865  
TITLE: Receptor that binds trail.  
AUTHOR(S): Rauch, Charles; Walczak, Henning (1)  
CORPORATE SOURCE: (1) Seattle, WA USA  
ASSIGNEE: Immunex Corporation  
PATENT INFORMATION: US 6072047 June 06, 2000  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (June 6, 2000) Vol. 1235, No. 1, pp.

No  
Pagination: e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
AB A protein designated TRAIL receptor binds the protein known as TNF-Related Apoptosis-Inducing Ligand (TRAIL). The TRAIL receptor finds use in purifying TRAIL or inhibiting activities thereof. Isolated DNA sequences encoding \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptides are provided, along with expression vectors containing the DNA sequences, and host cells transformed with such recombinant expression vectors. Antibodies that are immunoreactive with \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* are also provided.

L2 ANSWER 7 OF 41 WPIDS COPYRIGHT 2001  
DERWENT INFORMATION LTD  
ACCESSION NUMBER: 2000-358253 [51] WPIDS  
CROSS REFERENCE: 2000-256827 [22]  
DOC. NO. CPI: C2000-166232  
TITLE: Killing of tumor cells, e.g. solid tumors or carcinoma,  
comprises administration of synergistic combination of diterpenoid diepoxide and tumor necrosis factor related apoptosis-inducing ligand.  
DERWENT CLASS: B02  
INVENTOR(S): ROSEN, G D  
PATENT ASSIGNEE(S): (STRD) UNIV LELAND STANFORD JUNIOR  
COUNTRY COUNT: 22  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000048619 A1	20000824 (200051)*	EN	29		
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU					
MC NL PT SE					
W: AU CA JP SG					
AU 2000033658 A	20000904 (200103)				

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000048619 A1	WO 2000-US3891		
20000215			
AU 2000033658 A	AU 2000-33658	20000215	

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000033658 A	Based on	WO 200048619

PRIORITY APPLN. INFO: US 1999-120313 19990216  
AN 2000-358253 [51] WPIDS  
CR 2000-256827 [22]  
AB WO 200048619 A UPAB: 20001016  
NOVELTY - Method for enhanced killing of tumor cells comprises contacting a susceptible tumor cell with a synergistic mixture of a TRAIL (tumor necrosis factor (\*\*\*TNF\*\*\*) \*\*\*related\*\*\* \*\*\*apoptosis\*\*\* - \*\*\*inducing\*\*\* \*\*\*ligand\*\*\* ) \*\*\*receptor\*\*\* ligand and a diterpenoid triepoxide (I) in a combined dosage to kill at least 50 % of the cells.  
DETAILED DESCRIPTION - Method for enhanced

killing of tumor cells comprises contacting a susceptible tumor cell with a synergistic mixture of a TRAIL (tumor necrosis factor (\*\*\*TNF\*\*\*) \*\*\*related\*\*\* \*\*\*apoptosis\*\*\* - \*\*\*inducing\*\*\* \*\*\*ligand\*\*\* ) \*\*\*receptor\*\*\* ligand and a diterpenoid triepoxide of formula (I) in a combined dosage to kill at least 50 % of the cells.  
X1 = OH, =O or OR1;  
X2, X3 = OH, OR1 or H;  
R1 = C(O)-Y-Z;  
Y = 1-6C alkyl or alkenyl (sic);  
Z = COOR2, NR3R3' or N+R4R4'R4";  
R2 = a cation;  
R3, R3' = H or 1-6C alkyl, hydroxyalkyl or alkoxyalkyl;  
or  
R3+R3' = 5-7 membered heterocycle containing 2-6C, 1 or more N and optionally 1 or more O or S (optionally substituted by 1 or more R5, OR5, NR5R6, SR5, NO2, CN, COR5, CONSR6, F, Cl, Br or I);  
R5, R6 = H, lower alkyl, or lower alkenyl;  
R4, R4', R4" = 1-6C alkyl, hydroxyalkyl or alkoxyalkyl.  
ACTIVITY - Cytostatic. A combination of TRAIL (100 ng/ml) and triptolide (20 ng/ml) induced apoptosis in greater than 95 % of cells from solid tumor cell lines (e.g. lung, breast and sarcoma cell lines) while the individual components introduced apoptosis in less than 50 % of the cells.  
MECHANISM OF ACTION - TRAIL (tumor necrosis factor (\*\*\*TNF\*\*\*) \*\*\*related\*\*\* \*\*\*apoptosis\*\*\* - \*\*\*inducing\*\*\* \*\*\*ligand\*\*\* ) \*\*\*receptor\*\*\* ligand.  
USE - Killing tumor cells, especially a solid tumor or a carcinoma (especially mammary carcinoma or non-small cell lung carcinoma) (claimed).  
ADVANTAGE - The mixture is synergistic, so is active at lower doses and against otherwise resistant cell lines.  
Dwg.0/0

L2 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2000:753424 CAPLUS  
DOCUMENT NUMBER: 134:28070  
TITLE: Resistance to TRAIL-induced apoptosis in primitive neuroectodermal brain tumor cells correlates with a loss of caspase-8 expression  
AUTHOR(S): Grotzer, Michael A.; Eggert, Angelika; Zuzak, Tycho J.; Janss, Anna J.; Marwaha, Sunil; Wiewrodt, Barbara R.; Ikegaki, Naohiko; Brodeur, Garrett M.; Phillips, Peter C.  
CORPORATE SOURCE: Division of Oncology, The Children's Hospital of Philadelphia, Pennsylvania, PA, 19104, USA  
SOURCE: Oncogene (2000), 19(40), 4604-4610  
CODEN: ONCNE; ISSN: 0950-9232  
PUBLISHER: Nature Publishing Group  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB TNF-related apoptosis-inducing ligand (TRAIL) is a potent inducer of apoptosis in adult malignant glioma and various other human solid tumor models but not in normal tissues. To characterize the TRAIL death pathway in childhood primitive neuroectodermal brain tumor (PNET), 8 human PNET cell lines were tested for TRAIL-induced apoptosis. TRAIL-sensitivity of the PNET cell lines was correlated with mRNA expression levels of TRAIL, its agonistic (TRAIL-R1, TRAIL-R2) and antagonistic (TRAIL-R3, TRAIL-R4) receptors, cellular FLICE-like inhibitory protein (cFLIP), caspase-3 and caspase-8. Three of 8 PNET cell lines tested were susceptible to TRAIL-induced apoptosis. Sensitivity to TRAIL-induced apoptosis did not correlate with mRNA expression of TRAIL receptors or cFLIP. However, all TRAIL-sensitive PNET cell lines expressed caspase-8 mRNA and protein, while none of the five TRAIL-resistant PNET cell lines expressed caspase-8 protein. Treatment with the methyltransferase inhibitor 5-aza-2'-deoxycytidine restored mRNA expression of caspase-8 and

TRAIL-sensitivity in formerly TRAIL-resistant PNET cells, suggesting that gene methylation inhibits caspase-8 transcription in these cells. We conclude, that loss of caspase-8 mRNA is an important mechanism of TRAIL-resistance in PNET cells. Treatment with recombinant sol. TRAIL, possibly in combination with methyltransferase inhibitors, represents a promising therapeutic approach for PNET that deserves further investigation.  
REFERENCE COUNT: 40  
REFERENCE(S): (1) Ashkenazi, A; J Clin Invest 1999, V104, P155  
CAPLUS (2) Bodmer, J; Nat Cell Biol 2000, V2, P241  
CAPLUS (3) Degli-Esposti, M; J Exp Med 1997, V186, P1165  
CAPLUS (4) Eggert, A; Biotechniques 2000, V28, P681  
CAPLUS (5) Estrov, Z; Blood 1998, V92, P3090  
ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L2 ANSWER 9 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2000:702917 CAPLUS  
DOCUMENT NUMBER: 133:361874  
TITLE: Maturation of dendritic cells leads to up-regulation of cellular FLICE-inhibitory protein and concomitant down-regulation of death ligand-mediated apoptosis  
AUTHOR(S): Leverkus, Martin; Walczak, Henning; McLellan, Alex; Fries, Hans-Werner; Terbeck, Gabi; Brocker, Eva-B.; Kampgen, Eckhart  
CORPORATE SOURCE: Department of Dermatology, University of Wurzburg  
SOURCE: Medical School, Wurzburg, 97080, Germany  
Blood (2000), 96(7), 2628-2631  
CODEN: BLOOAW; ISSN: 0006-4971  
PUBLISHER: American Society of Hematology  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Dendritic cells (DCs) disappear from lymph nodes 1 to 2 days after antigen presentation, presumably by apoptosis. To evaluate the role of death ligands in elimination of DCs, we analyzed the sensitivity of human DCs to CD95 ligand (CD95L) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). We found mature DCs to be resistant to killing by CD95L or TRAIL, whereas only immature DCs were partially sensitive. However, all DC populations expressed CD95, TRAIL-R2, and TRAIL-R3 at comparable levels, suggesting that sensitivity to death ligand-induced DC apoptosis is not regulated at the receptor level. Interestingly, mature DCs highly expressed the caspase 8 inhibitory protein cFLIP, whereas only low levels were detected in immature DCs. Thus, death ligand sensitivity proved to be dependent on DC maturation and inversely correlated with expression levels of cFLIP. Induction of apoptosis by TRAIL or CD95L does not seem to play a role in the elimination of mature DCs, but instead might serve to regulate immature DC populations.  
REFERENCE COUNT: 26  
REFERENCE(S): (1) Ashkenazi, A; Curr Opin Cell Biol 1999, V11, P255

CAPLUS (3) Bjorck, P; Int Immunol 1997, V9, P365  
CAPLUS (4) Degli-Esposti, M; Immunity 1997, V7, P813  
CAPLUS (5) Djerbi, M; J Exp Med 1999, V190, P1025  
CAPLUS (6) Griffith, T; J Exp Med 1999, V189, P1343  
ALL CITATIONS AVAILABLE IN THE RE  
FORMAT  
L2 ANSWER 10 OF 41 SCISEARCH COPYRIGHT 2001 ISI (R)  
ACCESSION NUMBER: 2000:767008 SCISEARCH  
THE GENUINE ARTICLE: 3602D  
TITLE: Apoptosis mediators FasL and TRAIL are upregulated in

peripheral blood mononuclear cells in MS  
 AUTHOR: Huang W X (Reprint); Huang P; Gomes A; Hilbert J  
 CORPORATE SOURCE: HUDDINGE UNIV HOSP, DEPT NEUROL, KAROLINSKA INST, S-14186 HUDDINGE, SWEDEN (Reprint); KAROLINSKA INST, NOVUM, CTR BIOTECHNOL, HUDDINGE, SWEDEN  
 COUNTRY OF AUTHOR: SWEDEN  
 SOURCE: NEUROLOGY, (10 OCT 2000) Vol. 55, No. 7, pp. 928-934.

Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0028-3878.

DOCUMENT TYPE: Article; Journal  
 FILE SEGMENT: LIFE; CLIN  
 LANGUAGE: English  
 REFERENCE COUNT: 39

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Objective: To investigate the expression of apoptosis-inducing ligand and receptor molecules in patients with MS. Background: Dysregulation of apoptosis may induce autoimmune conditions, possibly through inadequate termination of immune responses, and could be of importance for pathogenesis of MS. Methods: Messenger RNA (mRNA) levels of two apoptosis-related members of the tumor necrosis factor (TNF) receptor family, Fas and TNF-related apoptosis-inducing ligand (TRAIL) receptor 2 (\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -2), and their ligands, Fas ligand (FasL) and TRAIL, were quantified by competitive reverse transcription PCR in unstimulated peripheral blood mononuclear cells in 47 untreated patients with MS and 46 control subjects. Results: The expression of FasL was increased in patients with MS compared with healthy control subjects.

Analysis of clinical subgroups revealed that the increase was marked in relapsing-remitting MS, being especially high in remission (p = 0.0002), but less so in chronic progressive MS (p = 0.14). Compared with healthy control subjects, TRAIL mRNA levels were also upregulated in patients with MS (p = 0.0001) but did not differ between clinical subgroups. The expression of \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -2, was slightly elevated in patients with MS (p = 0.02) whereas the expression of Fas was similar in patients and control subjects. The ratio of expression levels for two isoforms of \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -2, TRICK2a and TRICK2b, in patients with MS differed from healthy control subjects (p = 0.04).

Conclusions: There was increased expression of both FasL and TRAIL in peripheral blood lymphocytes. It remains to be determined whether this increased expression represents a disease-promoting autoimmune process or is merely the effect of a secondary compensatory mechanism that downregulates the inflammatory response.

L2 ANSWER 11 OF 41 MEDLINE  
 DUPLICATE 2  
 ACCESSION NUMBER: 2000338587 MEDLINE  
 DOCUMENT NUMBER: 20338587 PubMed ID: 10881678  
 TITLE: Extensive lymphopenia due to apoptosis of uninfected

lymphocytes in acute measles patients.  
 AUTHOR: Okada H; Kobune F; Sato T A; Kohama T; Takeuchi Y; Abe T; Takayama N; Tsuchiya T; Tashiro M  
 CORPORATE SOURCE: Department of Viral Diseases and Vaccine Control, National Institute of Infectious Diseases, Tokyo, Japan.  
 SOURCE: ARCHIVES OF VIROLOGY, (2000) 145 (5) 905-20.

Journal code: 8L7; 7506870. ISSN: 0304-8608.  
 PUB. COUNTRY: Austria  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200007  
 ENTRY DATE: Entered STN: 20000728  
 Last Updated on STN: 20000728  
 Entered Medline: 20000720

AB Infection with measles virus induces a transient

immunosuppression, which occasionally results in fatal opportunistic infections. To obtain fundamental information about the mechanism, we examined peripheral blood mononuclear cells (PBMC) from acute measles patients aged from infants to 35 years old, obtained at various times from incubation periods to 103 days after onset of rash, for the number of lymphocyte subsets by flowcytometry. The data were analyzed for relationships between aging of the patients and the severity of immunosuppression. In classical measles cases, infected lymphocytes detected as a minor population during the incubation period disappeared soon after onset of rash, whereas in the cases of serious illness, the infected cells persisted longer after the rash. At the onset of rash, remarkable lymphopenia had already occurred in all measles cases with reduction in cell numbers of CD4+ T cells, CD8+ T cells, B cells, neutrophils, and monocytes. In contrast, natural killer (NK) cells were increased in number and activated, which might be a response compensatory for the lymphopenia. Apoptosis-associated molecules such as CD95(Fas) and \*\*\*TNF\*\*\* - \*\*\*related\*\*\* - \*\*\*apoptosis\*\*\* - \*\*\*inducing\*\*\* - \*\*\*ligand\*\*\* - \*\*\*receptor\*\*\* (\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -2) were highly expressed on the cell surface of most surviving non-infected lymphocytes, and DNA fragmentation was also observed upon incubation in vitro. These results suggested that the profound lymphopenia was primarily due to extended death of non-infected blood cells caused by apoptosis. The severity and duration of the lymphopenia were age-dependent; less severe in young children whereas much severer in infants under one year of age as well as adolescents and adults. From these results, it was suggested that remarkable lymphopenia due to apoptosis of uninfected cells is one of the principal causes for immunosuppression induced by measles virus infection, and is correlated with the age-dependent severity of the disease.

L2 ANSWER 12 OF 41 SCISEARCH COPYRIGHT 2001 ISI (R)  
 ACCESSION NUMBER: 2000-949420 SCISEARCH  
 THE GENUINE ARTICLE: 357JU  
 TITLE: Expression of TRAIL/ \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* in inflammatory myopathies.

AUTHOR: Murakawa Y (Reprint); Kondo M; Kayagaki N; Kawakami M; Okumura K; Kobayashi S  
 SOURCE: ARTHRITIS AND RHEUMATISM, (SEP 2000) Vol. 43, No. 9, Supp. [S], pp. 775-775.  
 Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 0004-3591.

DOCUMENT TYPE: Conference; Journal  
 FILE SEGMENT: LIFE; CLIN  
 LANGUAGE: English  
 REFERENCE COUNT: 0

L2 ANSWER 13 OF 41 CAPLUS COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 2000-583433 CAPLUS  
 DOCUMENT NUMBER: 134-146230  
 TITLE: Expression of TRAIL receptors in human autoreactive

and foreign antigen-specific T cells  
 AUTHOR(S): Wending, U.; Walczak, H.; Dorr, J.; Jaboc, C.; Weller, M.; Krammer, P. H.; Zipp, F.  
 CORPORATE SOURCE: Division of Neuroimmunology, Department of Neurology, Charite, Berlin, Germany  
 SOURCE: Cell Death Differ. (2000), 7(7), 637-644  
 CODEN: CDDIEK; ISSN: 1350-9047  
 PUBLISHER: Nature Publishing Group  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Deletion of T cells due to apoptosis induction is a regulatory mechanism in the human immune system that may be impaired in autoimmune diseases

such as multiple sclerosis (MS). Involvement of the apoptosis-mediating CD95/CD95 ligand system in MS has been demonstrated. Here, the authors report that (auto)antigen-specific human T cells are not killed in vitro by sol. TNF-related apoptosis-inducing ligand (TRAIL) although expressing death-inducing receptors, TRAIL receptor 1 (TRAIL-R1) and TRAIL-R2.

Apoptosis was assessed by caspase activation and DNA fragmentation, receptor expression was detected by RT-PCR and flow cytometry. The (auto)antigen-specific T cells were also resistant to specific TRAIL-R1/TRAIL-R2-directed induction of apoptosis, indicating that coexpression of the truncated TRAIL-R3 and TRAIL-R4 in these T cells is not responsible for the obsd. resistance. Upon stimulation, levels of death-inducing TRAIL receptors decreased whereas TRAIL was up-regulated on the cell surface. In contrast to CD95, the role of TRAIL receptors in MS might not involve regulation of T cell vulnerability.  
 REFERENCE COUNT: 51  
 REFERENCE(S): (1) Alderson, M; J Exp Med 1995, V181, P71 CAPLUS

(2) Cusani, E; J Neuroimmunol 1998, V82, P5  
 CAPLUS  
 (3) Critchfield, J; Science 1994, V263, P1139  
 CAPLUS  
 (4) Degli-Esposti, M; Immunity 1997, V7, P813  
 CAPLUS  
 (5) Degli-Esposti, M; J Exp Med 1997, V186, P1165

CAPLUS  
 ALL CITATIONS AVAILABLE IN THE RE  
 FORMAT

L2 ANSWER 14 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 2000-238935 BIOSIS  
 DOCUMENT NUMBER: PREV200000238935  
 TITLE: Expression and function of the TRAIL ligand/receptor system in neuroblastoma.

AUTHOR(S): Eggert, Angelika (1); Zuzak, T. (1); Grotzer, M. A. (1); Ikegaki, N. (1); Brodeur, G. M. (1)  
 CORPORATE SOURCE: (1) Children's Hosp of Philadelphia, Philadelphia, PA USA  
 SOURCE: Proceedings of the American Association for Cancer Research  
 Annual Meeting, (March, 2000) No. 41, pp. 557.  
 Meeting Info: 91st Annual Meeting of the

American Association for Cancer Research, San Francisco, California, USA April 01-05, 2000  
 ISSN: 0197-016X.

DOCUMENT TYPE: Conference  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L2 ANSWER 15 OF 41 MEDLINE  
 DUPLICATE 3  
 ACCESSION NUMBER: 2000139806 MEDLINE  
 DOCUMENT NUMBER: 20139806 PubMed ID: 10676636  
 TITLE: Regulation of tumor necrosis factor-related apoptosis-inducing ligand sensitivity in primary and transformed human keratinocytes.

AUTHOR: Leverkus M; Neumann M; Mengling T; Rauch C T; Brocker E B; Krammer P H; Walczak H  
 CORPORATE SOURCE: Department of Dermatology, University of Wurzburg Medical School, Germany.  
 SOURCE: CANCER RESEARCH, (2000 Feb 1) 60 (3) 553-9.

Journal code: CNF; 2984705R. ISSN: 0008-5472.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200002  
 ENTRY DATE: Entered STN: 20000314  
 Last Updated on STN: 20000810  
 Entered Medline: 20000228

AB Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been shown to exert potent cytotoxic activity against many tumor cell lines but not against normal cells. It has been hypothesized that this difference in TRAIL sensitivity between normal and transformed cells might be due to the expression of the non-death-inducing TRAIL receptors (\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -2)

\*\*\*R\*\*\* ) TRAIL-R3 and TRAIL-R4, presumably by competition for limited amounts of TRAIL. To assess the regulation of resistance versus sensitivity to TRAIL in primary as well as transformed keratinocytes, we examined TRAIL sensitivity, TRAIL receptor expression, and intracellular signaling events induced by TRAIL. Although TRAIL induced apoptosis in primary as well as transformed keratinocytes, a marked difference in sensitivity could be observed with primary keratinocytes (PK) being 5-fold less sensitive to TRAIL than transformed keratinocytes (TK). Yet both cell types exhibited similar TRAIL receptor surface expression, suggesting that expression of TRAIL-R3 and TRAIL-R4 may not be the main regulator of sensitivity to TRAIL. Biochemical analysis of the signaling events induced by TRAIL revealed that PK could be sensitized for TRAIL and, similarly, for TRAIL-R1- and TRAIL-R2-specific apoptosis by pretreatment of the cells with cycloheximide (CHX). This sensitization concomitantly resulted in processing of caspase-8, which did not occur in TRAIL-resistant PK. These data indicate that an early block of TRAIL-induced apoptosis was present in PK compared with TK or PK treated with CHX. Interestingly, cellular FLICE inhibitory protein (cFLIP) levels, high in PK and low in TK and several other squamous cell carcinoma cell lines, decreased rapidly after treatment of PK with CHX, correlating with the increase in TRAIL sensitivity and caspase-8 processing. Furthermore, ectopic expression of cFLIP long (cFLIP(L)) in TK by transfection with a cFLIP(L) expression vector resulted in resistance to TRAIL-mediated apoptosis of these cells. Thus, our results demonstrate that TRAIL sensitivity in PK is primarily regulated at the intracellular level rather than at the receptor level.

L2 ANSWER 16 OF 41 MEDLINE  
 DUPLICATE 4  
 ACCESSION NUMBER: 2000427861 MEDLINE  
 DOCUMENT NUMBER: 20417933 PubMed ID: 10960439  
 TITLE: Chemotherapeutic agents augment TRAIL-induced apoptosis in human hepatocellular carcinoma cell lines.  
 AUTHOR: Yamanaka T; Shiraki K; Sugimoto K; Ito T; Fujikawa K; Ito M; Takase K; Moriyama M; Nakano T; Suzuki A  
 CORPORATE SOURCE: First Department of Internal Medicine, Mie University School of Medicine, Tsu, Japan.  
 SOURCE: HEPATOLOGY, (2000 Sep) 32 (3) 482-90.  
 Journal code: GBZ; 8302946. ISSN: 0270-9139.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200009  
 ENTRY DATE: Entered STN: 20000922  
 Last Updated on STN: 20000922  
 Entered Medline: 20000914

AB TNF-related apoptosis-inducing ligand (TRAIL) selectively induces apoptosis in various transformed cell lines but not in almost-normal tissues. It is regulated by 2 death receptors, TRAIL receptor 1 (TRAIL-R1) and TRAIL-R2, and 2 decoy receptors, TRAIL-R3 and TRAIL-R4. We investigated the expression of \*\*\*TRAIL\*\*\* . \*\*\*R\*\*\* and TRAIL-induced apoptosis in human hepatocellular carcinomas (HCCs). TRAIL-R1, -R2, and -R4 were expressed in 6 HCC cell lines examined, but TRAIL-R3 was expressed in only 2 of the 6 cell lines. In addition, immunohistochemical results revealed a high and prevalent expression of TRAIL-R1 and -R2 in human HCC tissues. Despite the expression of TRAIL-R1 and -R2, all 6 HCC cell lines showed resistance to TRAIL-induced apoptosis with no relation to nuclear factor kappa B (NF-kappaB) levels induced by TRAIL. TRAIL-induced death signal was inhibited with both decreased

caspase-8 and caspase-3 activity. However, TRAIL induced significant apoptosis in the presence of a subtoxic level of actinomycin D, indicating that the TRAIL-induced apoptotic pathway is in place in these cell lines. In addition, we found that treatment with conventional chemotherapeutic agents, doxorubicin and camptothecin, dramatically augmented TRAIL-induced cytotoxicity in most of the HCC cell lines. Actinomycin D and camptothecin almost completely suppressed NF-kappaB induction by TRAIL, whereas doxorubicin had little effect. These results indicate that TRAIL, in combination with chemotherapeutic agents, may have therapeutic potential in the treatment of human HCC.

L2 ANSWER 17 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
 DUPLICATE 5  
 ACCESSION NUMBER: 2001:127375 BIOSIS  
 DOCUMENT NUMBER: PREV200100127375  
 TITLE: Expression of different receptors of the apoptosis inducing gene TRAIL in human ovarian tumors.  
 AUTHOR(S): Li Xin-guo (1); Zhang Yu (1); Chen Bing-lai (1)  
 CORPORATE SOURCE: (1) Department of Gynecology and Obstetrics, Xiangya Hospital, Hunan Medical University, Changsha, 410008 China  
 SOURCE: Hunan Yike Daxue Xuebao, (Oct. 28, 2000) Vol. 25, No. 5, pp. 471-473. print.  
 ISSN: 1000-5625.  
 DOCUMENT TYPE: Article  
 LANGUAGE: Chinese  
 SUMMARY LANGUAGE: Chinese; English  
 AB Reverse transcriptase polymerase chain reaction (RT-PCR) was applied to assay mRNA expression of TRAIL (the \*\*\*TNF\*\*\* \*\*\*related\*\*\* \*\*\*apoptosis\*\*\* \*\*\*inducing\*\*\* \*\*\*ligand\*\*\* ) \*\*\*receptors\*\*\* (DR5, DR1, and DR2) in 3 cases of normal ovarian tissues, 6 cases of ovarian benign tumors, and 16 cases of ovarian cancers. Peripheral blood lymphocytes were used as a positive control. Positive expression of the DR5 and DR1 were found in peripheral blood lymphocytes and 3 cases of normal ovaries. Positive expressions of the DR5 and DR1 were 83.3% (5/6) in benign ovarian tumors and 68.8% (11/16) in ovarian cancers respectively. Positive expression of the DR2 was only found in normal ovaries and benign tumors. These findings suggest that expression of different receptors may play an important role in the apoptosis regulation of ovarian tumors, especially DR2.

L2 ANSWER 18 OF 41 SCISEARCH COPYRIGHT 2001  
 ISI (R) DUPLICATE 6  
 ACCESSION NUMBER: 2000:894211 SCISEARCH  
 THE GENUINE ARTICLE: 375MJ  
 TITLE: Expression of TRAIL ( \*\*\*TNF\*\*\* - \*\*\*related\*\*\* \*\*\*apoptosis\*\*\* . \*\*\*inducing\*\*\* \*\*\*Ligand\*\*\* ) \*\*\*receptors\*\*\* in cervical cancer  
 AUTHOR: Ryu H S; Chang K H (Reprint); Chang S J; Kim M S; Joo H J; Oh K S  
 CORPORATE SOURCE: AJOU UNIV, SCH MED, DEPT OBSTET & GYNECOL, SAN 5, SUWON 44721, SOUTH KOREA (Reprint); AJOU UNIV, SCH MED, DEPT OBSTET & GYNECOL, SUWON 44721, SOUTH KOREA; AJOU UNIV, SCH MED, DEPT PATHOL, SUWON 44721, SOUTH KOREA  
 COUNTRY OF AUTHOR: SOUTH KOREA  
 SOURCE: INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER, (SEP-OCT 2000) Vol. 10, No. 5, pp. 417-424.  
 Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.  
 ISSN: 1048-891X.  
 DOCUMENT TYPE: Article; Journal  
 FILE SEGMENT: CLIN  
 LANGUAGE: English  
 REFERENCE COUNT: 35  
 \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Apoptosis is an intrinsic and fundamental biologic process that plays a critical role in the normal development of multicellular organisms and in the maintenance of tissue homeostasis. Some of the well known regulators of apoptosis are cytokines of the tumor necrosis factor (TNF) ligand family, such as Fas ligand (Fas L) and TNF, which induce apoptosis by activation of their corresponding receptors, Fas and TNFR-1. Recently, a new member of the TNF family known as TRAIL (TNF-related apoptosis-inducing ligand) was identified and shown to induce p53-independent apoptosis in a variety of tumor cell lines but not in normal cells. Four human receptors for TRAIL were also recently identified and designated TRAIL-R1, -R2, -R3, and -R4. The aim of this study is to examine whether TRAIL and TRAIL receptors (-R1, -R2, -R3) are expressed in uterine cervical cancer and whether it is correlated with apoptosis, TRAIL, and TRAIL receptors. The subjects were 20 patients who were diagnosed with cervical cancer. Western blotting was performed in nine cases and immunohistochemical staining for TRAIL and TRAIL-R1, -R2, and -R3 was performed in 11 cases. There were proteins for TRAIL, TRAIL-R1, -R2, and -R3 in tissues from cervical cancer. All TRAIL receptors were expressed in both normal cervical epithelium and tumor cells, and TRAIL-R1 and -R2 were more strongly expressed in tumor cells than normal epithelium (P < 0.05). Apoptosis correlated with expression of TRAIL-R1 and -R2 (P < 0.05). This study suggests that TRAIL induces apoptosis in cervical cancer through its receptors.

L2 ANSWER 19 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 2000:252329 BIOSIS  
 DOCUMENT NUMBER: PREV200000252329  
 TITLE: Inhibition of NF-kappaB activity enhances trail induced apoptosis in breast cancer cell lines.  
 AUTHOR(S): Keane, Macon M. (1); Rubinstein, Yaffa R. (1); Ettenberg, Seth A. (1); Nau, Marion M. (1); Lipkowitz, Stan (1)  
 CORPORATE SOURCE: (1) National Cancer Inst, Bethesda, MD USA  
 SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 244.  
 Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000  
 ISSN: 0197-016X.  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English

L2 ANSWER 20 OF 41 SCISEARCH COPYRIGHT 2001  
 ISI (R)  
 ACCESSION NUMBER: 2000:790597 SCISEARCH  
 THE GENUINE ARTICLE: 363RA  
 TITLE: Mechanisms of resistance of normal cells to TRAIL induced apoptosis vary between different cell types  
 AUTHOR: Zhang X D; Nguyen T; Thomas W D; Sanders J E; Hersey P (Reprint)  
 CORPORATE SOURCE: NEWCASTLE MATER HOSP, IMMUNOL & ONCOL UNIT, DAVID MADDISON BLDG, ROOM 443, CNR KING & WATT ST, NEWCASTLE, NSW 2300, AUSTRALIA (Reprint); NEWCASTLE MATER HOSP, IMMUNOL & ONCOL UNIT, NEWCASTLE, NSW 2300, AUSTRALIA  
 COUNTRY OF AUTHOR: AUSTRALIA  
 SOURCE: FEBS LETTERS, (6 OCT 2000) Vol. 482, No. 3, pp. 193-199.  
 Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.  
 ISSN: 0014-5793.  
 DOCUMENT TYPE: Article; Journal  
 FILE SEGMENT: LIFE  
 LANGUAGE: English

# REFERENCE COUNT: 33

## \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

**AB** Resistance of normal cells to tumour necrosis factor related apoptosis inducing ligand (TRAIL) induced apoptosis is believed to be mediated by expression of two decoy receptors. Here we show that the expression and localisation of TRAIL receptors (TRAIL-Rs) vary between different cells and that resistance to TRAIL is mediated by different mechanisms. The decoy receptor, TRAIL-R3, appeared important in protection of endothelial cells, whereas lack of surface death receptor expression and as yet unknown intracellular inhibitor(s) of apoptosis downstream of caspase-3 may play a major role in protection of melanocytes and fibroblasts from TRAIL induced apoptosis, respectively. Differential subcellular location of decoy receptors may be an important determinant of their effectiveness in different types of normal cells. (C) 2000 Federation of European Biochemical Societies. Published by Elsevier Science B.V. All rights reserved.

L2 ANSWER 21 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2001:300248 BIOSIS  
DOCUMENT NUMBER: PREV200100300248

**TITLE:** Variations in trail-induced apoptosis of freshly obtained

myeloma cells are not related to trail receptor expression or prior chemotherapy.

**AUTHOR(S):** Linez, Lisa F. (1); Yeh, Te-Hsien; Enno, Arno (1); Spencer, Andrew

**CORPORATE SOURCE:** (1) Hunter Haematology Research Group, Mater Misericordiae

Hospital, Newcastle, NSW Australia  
**SOURCE:** Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp.

162a. print.  
Meeting Info.: 42nd Annual Meeting of the

American Society of Hematology San Francisco, California, USA

**December** 01-05, 2000 American Society of Hematology  
ISSN: 0006-4971.

**DOCUMENT TYPE:** Conference

**LANGUAGE:** English

**SUMMARY LANGUAGE:** English

**AB** TNF-related apoptosis-inducing ligand (TRAIL) is a potent and selective inducer of apoptosis in malignant cells. Using the combined methods of

Annexin V labelling, cell cycle analysis and DNA electrophoresis, we have demonstrated susceptibility to TRAIL-induced apoptosis in the human

multiple myeloma (MM) cell lines NCI H929, RPMI 8226, OPM-2 and LP-1, while the lymphoblastoid cell lines (LCL) U266 and MC/CAR were resistant.

Two different forms of TRAIL were tested: purified human recombinant

soluble TRAIL (s-TRAIL; residues 114-281; Biomol, Plymouth Meeting, PA)

demonstrated maximal apoptosis induction at 1 mug/ml in sensitive cell

lines, while a leucine zipper construct (LZ-TRAIL; Immunex Corp., Seattle,

WA) was equally effective when used at a concentration of 500 ng/ml. BM

samples obtained from 16 MM patients at various stages of disease were

incubated for 24 hours with or without either 2mug/ml s-TRAIL (n=8) or

1mug/ml LZ-TRAIL (n=8). The percentage of viable MM cells was then

determined by flow cytometric quantification of anti-CD138 stained cells

and relative TRAIL-induced reduction in MM cells calculated using the

formula: ((Untreated)-(TRAIL-Treated))/Untreated X 100%. BM samples from 6

of 16 (38%) patients demonstrated a significant (>10%) relative reduction

in the number of MM cells following TRAIL incubation (range: 11% to 59%).

This did not correlate with prior therapy, as a reduction was seen in 2/5

samples obtained from patients at diagnosis, 2/5 samples following

standard-dose chemotherapy and 2/6 samples following

high-dose chemotherapy. The relationship between TRAIL-receptor expression (TRAIL-R1, R2, R3, R4 and OPG) and TRAIL-induced apoptosis was examined in 2 sensitive (NCI H929, RPMI 8226) and the 2 resistant cell lines and 5 MM

BM samples (2 sensitive, 3 resistant) utilising RT-PCR and surface

immunostaining of purified MM cells. Concordance between TRAIL-receptor

mRNA detection and cell surface expression was shown in all cell lines.

Furthermore, all cell lines and patient samples demonstrated mRNA

expression for the intracellular death-domain containing TRAIL-R1.

Variable expression of the 2 decoy (TRAIL-R3 and R4) and soluble (OPG)

receptors was seen and this did not correlate with TRAIL sensitivity. We

conclude that MM cell expression of death effector receptors for TRAIL is

insufficient to confer sensitivity to TRAIL-induced apoptosis but that in

a significant minority of patients, irrespective of prior therapy, MM

cells are sensitive to TRAIL-induced apoptosis.

L2 ANSWER 22 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2000:249346 CAPLUS  
DOCUMENT NUMBER: 133:220794

**TITLE:** Expression of Trail receptor on human T cells and

apoptosis induced by trail

**AUTHOR(S):** Fan, Xuegong

**CORPORATE SOURCE:** Department of Infectious Diseases, Xiangya Hospital,

Hunan Medical University, Changsha, 410008, Peop. Rep.

China

**SOURCE:** Zhongguo Mianyixue Zazhi (2000), 16(3), 122-124

**CODEN:** ZMAZEE; ISSN: 1000-484X

**PUBLISHER:** Zhongguo Mianyixue Zazhi Bianjibu

**DOCUMENT TYPE:** Journal

**LANGUAGE:** Chinese

**AB** The expression of Trail ( \*\*\*TNF\*\*\* - \*\*\*related\*\*\* \*\*\*apoptosis\*\*\*

\*\*\*inducing\*\*\* \*\*\*ligand\*\*\* ) \*\*\*receptor\*\*\* on human T cells

and apoptosis induced by Trail were studied. The pos. cells for Trail

receptor and apoptotic cells were detd. by flow cytometry. Trail receptor

on unstimulated Jurkat cells was found in % and the stimulation could not

increase the expression of Trail receptor on Jurkat cells. The apparent

apoptosis of Jurkat cells was found in (90.01 +/- 26.71)%. Peripheral

blood lymphocytes (PBL) from healthy donors may express Trail receptor

after activation (25.27 +/- 6.42)%, but no apoptosis was obsd. in these

PBL. Human T cells may express Trail receptor. The ligation of Trail

receptor and Trail plays an important role in regulation of apoptosis.

L2 ANSWER 23 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:382776 BIOSIS  
DOCUMENT NUMBER: PREV200000382776

**TITLE:** Coordinated regulation of two

TRAIL-R2/KILLER/DR5 mRNA

isoforms by DNA damaging agents, serum and 17beta-estradiol

in human breast cancer cells.

**AUTHOR(S):** Wang, Thomas T. Y. (1); Jeng, Jüingjau

**CORPORATE SOURCE:** (1) Phytonutrients Laboratory, Beltsville Human Nutrition

Research Center, ARS, USDA, Building 307, Room 326,

Beltsville, MD, 20705 USA

**SOURCE:** Breast Cancer Research and Treatment, (May, 2000) Vol. 61,

No. 1, pp. 87-96. print.

ISSN: 0167-6806.

**DOCUMENT TYPE:** Article

**LANGUAGE:** English

**SUMMARY LANGUAGE:** English

**AB** A search of the Genebank database revealed that there are two distinct

gene sequences with the common name of

TRAIL-R2/Killer/DR5. Using reverse

transcription-polymerase chain reaction (RT-PCR), we confirmed the

existence of two isoforms of TRAIL-R2/Killer/DR5 mRNA, which we have

designated the long and short isoforms based on their

electrophoretic mobility. We found that both the long and short mRNA isoforms are

ubiquitously expressed in human tissues and cell lines. The long form

generally predominates, but the proportion of the two isoforms varies

depending on the tissue type. Treatment of MCF-7 human breast cancer cells

with the DNA damaging drugs adriamycin, camptothecin, or etoposide causes

a coordinated up-regulation of both isoforms. Treatment of the p53-mutant

T-47D breast cancer cell line with adriamycin also results in up-regulation of both isoforms, suggesting that adriamycin

up-regulates TRAIL-R2/Killer/DR5 expression independent of functional p53. The

expression of both mRNA isoforms are increased in MCF-7 cells cultured in

charcoal-stripped fetal bovine serum compared to normal serum, suggesting

that sex steroid hormones may play a role in the negative regulation of

their expression. This was confirmed in MCF-7 cells cultured in stripped

serum supplemented with 17beta-estradiol, which also resulted in a

decrease in the mRNA expression of both isoforms. These results

demonstrate that the TRAIL-R2/Killer/DR5 gene gives rise to two distinct

forms of mRNA, and that these two forms are coordinately regulated by DNA

damage and 17beta-estradiol in human breast cancer cells. The functional

significance of the two isoforms remains to be determined.

L2 ANSWER 24 OF 41 CAPLUS COPYRIGHT 2001 ACS  
ACCESSION NUMBER: 2000:656238 CAPLUS  
DOCUMENT NUMBER: 133:250528

**TITLE:** Fas- and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -induced apoptosis

is blocked by Bcl-xL in pancreatic carcinoma cells

**AUTHOR(S):** Ungefroren, H.; Hinz, S.; Bonecke, L.; Klosa, K.;

Kalthoff, H.

**CORPORATE SOURCE:** Forschungsgruppe Molekulare Onkologie, Klinik für

Allgemeine Chirurgie und Thoraxchirurgie, Christian-Albrechts-Universität, Kiel, D-24105, Germany

**SOURCE:** Chir. Forum Exp. Klin. Forsch. (2000) 65-68

**CODEN:** CFEKA7; ISSN: 0303-6227

**PUBLISHER:** Springer-Verlag

**DOCUMENT TYPE:** Journal

**LANGUAGE:** German

**AB** The resistance of pancreatic adenocarcinomas to std. chemo- and

radiotherapy results from perturbations in apoptosis. In this study the

authors tried to identify proteins that interfere neg. with the signal

transduction of the Fas (CD95, APO-1) and TRAIL receptors, resp. 3

Different pancreatic carcinoma cell lines and Colo357 cells retrovirally

transduced with a Bcl-xL expression vector were treated with the agonistic

anti-Fas antibody CH11 or with TRAIL in the presence or absence of

cycloheximide. Subsequently, apoptosis was measured with the JAM DNA

fragmentation assay. All pancreatic carcinoma cell lines investigated

displayed cross-resistance against Fas- and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*

-induced apoptosis which could to various extents be alleviated by

cycloheximide treatment. Overexpression of Bcl-xL in the more sensitive

cell line Colo357 rendered these cells completely resistant to Fas- and

\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* -induced apoptosis. High Bcl-xL expression in

pancreatic carcinoma is not only responsible for resistance to std. chemo-

and radiotherapy but also represents an immune escape mechanism leading to

a survival advantage of tumor cells. Inhibition of the anti-apoptotic

function of Bcl-xL therefore offers an interesting therapeutic option.

**REFERENCE COUNT:** 3

**REFERENCE(S):** (1) Ashkenazi, A; J Clin Invest 1999, V104, P155

CAPLUS  
(2) Scaffidi, C; EMBO J 1998, V17, P1675

## CAPLUS

(3) Ungefren, H; Cancer Res 1998, V58,  
P1741 CAPLUS

L2 ANSWER 25 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
ACCESSION NUMBER: 2000:276014 BIOSIS  
DOCUMENT NUMBER: PREV200000276014  
TITLE: Resistance to trail-mediated apoptosis in  
human

hepatocellular carcinomas.  
AUTHOR(S): Yamanaka, Takenari (1); Shiraki, Katsuya  
(1); Inoue, Hidekazu (1); Ito, Takeshi (1); Sugimoto, Kazushi  
(1);

Sakai, Takahisa (1); Ohmori, Shigeru (1);  
Wegayama, Hidetaka (1); Fujikawa, Katsuhiko (1); Takase,  
Koujiro (1); Nakano, Takeshi (1)

CORPORATE SOURCE: (1) First Dept of Internal Medicine,  
Mie Univ, Tsu Japan  
SOURCE: Gastroenterology, (April, 2000) Vol. 118,  
No. 4 Suppl. 2

Part 1, pp. AASLD A910. print.  
Meeting Info.: 101st Annual Meeting of the  
American Gastroenterological Association and the Digestive  
Disease Week. San Diego, California, USA May 21-24,  
2000 American

Gastroenterological Association  
ISSN: 0016-5085.

DOCUMENT TYPE: Conference  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L2 ANSWER 26 OF 41 WPIDS COPYRIGHT 2001  
DERWENT INFORMATION LTD DUPLICATE

ACCESSION NUMBER: 1999-276942 [23] WPIDS  
CROSS REFERENCE: 1999-229238 [19]  
DOC. NO. CPI: C1999-081240  
TITLE: Novel tumor necrosis factor receptor proteins  
TRAIL-R2

and TRAIL-R3.  
DERWENT CLASS: B04 D16  
INVENTOR(S): TSCHOPP, J  
PATENT ASSIGNEE(S): (BIOI) BIOGEN INC; (APOT-N)  
APOTEC R & D SA  
COUNTRY COUNT: 83  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9912963	A2	19990318	(199923)*	EN	28
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM					
GR IE IT KE LS LU MC MW NL					
OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN					
CU CZ DE DK EE ES FI GB GE					
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK					
LR LS LT LU LV MD MG					
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI					
SK SL TJ TM TR TT UA UG					
US UZ VN YU ZW					
AU 9893863	A	19990329	(199932)		
EP 1012179	A2	20000628	(200035)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI					
LT LU LV MC MK NL PT					
RO SE SI					

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9912963	A2	WO 1998-US19029	19980911
AU 9893863	A	AU 1998-93863	19980911
EP 1012179	A2	EP 1998-946966	19980911
		WO 1998-US19029	19980911

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9893863	A Based on	WO 9912963
EP 1012179	A2 Based on	WO 9912963

PRIORITY APPLN. INFO: US 1998-84422 19980506; US  
1997-58631

19970912  
AN 1999-276942 [23] WPIDS  
CR 1999-229238 [19]

AB WO 9912963 A UPAB: 20000725  
NOVELTY - Novel mammalian cysteine-rich receptors of  
the tumour necrosis  
factor family TRAIL-R2 and TRAIL-R3 proteins have the  
440 and 259 amino  
acid sequences given in the specification respectively.  
DETAILED DESCRIPTION - INDEPENDENT  
CLAIMS are included for: (1)

antibody preparation reactive to TRAIL-R2 or -R3 or  
biologically active  
fragment; (2) a soluble \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*  
comprising a human  
immunoglobulin Fc domain; and (3) a method of expressing  
TRAIL-R2 or -R3  
in a mammalian cell by introducing the TRAIL-R2 or  
-R3-encoding DNA into a  
cell and expressing the TRAIL-R2 or -R3 in the cell.  
ACTIVITY - Cytostatic; anti-apoptosis;  
immunomodulator.  
MECHANISM OF ACTION - Tumour necrosis factor  
receptor blocker.  
USE - The TRAIL-R2 or -R3 can be used for treating or  
reducing the  
advancement, severity or effects of an immunological  
disease in a mammal,  
or for treating cancer or for inducing cell death.  
Dwg.0/5

L2 ANSWER 27 OF 41 WPIDS COPYRIGHT 2001  
DERWENT INFORMATION LTD DUPLICATE

ACCESSION NUMBER: 1999-132236 [11] WPIDS  
DOC. NO. CPI: C1999-038767  
TITLE: New isolated TRAIL receptor polypeptides -  
used to

develop products for treating e.g. thrombotic  
microangiopathy, multiple sclerosis, systemic  
lupus

erythematous or HIV infection.  
DERWENT CLASS: B04 D16  
INVENTOR(S): DEGLI-ESPOSTI, M  
PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP  
COUNTRY COUNT: 28  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
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WO 9903992	A1	19990128	(199911)*	EN	50
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU					
MC NL PT SE					
W: AU CA IL IS JP KR MX NO NZ					
AU 9883957	A	19990210	(199925)		
EP 998561	A1	20000510	(200027)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU					
MC NL PT SE					

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9903992	A1	WO 1998-US14410	19980710
AU 9883957	A	AU 1998-83957	19980710
EP 998561	A1	EP 1998-934441	19980710
		WO 1998-US14410	19980710

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9883957	A Based on	WO 9903992
EP 998561	A1 Based on	WO 9903992

PRIORITY APPLN. INFO: US 1997-892119 19970715  
AN 1999-132236 [11] WPIDS  
AB WO 9903992 A UPAB: 19990316  
An isolated DNA (A) comprises a nucleotide sequence (NS)  
encoding tumour  
necrosis factor (TNF)-Related Apoptosis-Inducing ligand  
(TRAIL) receptor  
polypeptide ( \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* ), where the  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* is selected from: (a) a \*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* polypeptide  
(I) having a sequence (S1) of 386 amino acids (aa); (b) a  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* polypeptide (II) having a 386 aa sequence (S2),  
and (c) a  
fragment of a polypeptide of (a) or (b), where the fragment  
is capable of  
binding TRAIL. Also claimed are: (1) an isolated DNA  
encoding a  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptide which comprises  
an aa sequence that  
is at least 90% identical to an aa sequence selected from: (a)  
aa residues  
1-386, 56-386, 1-211, or 56-211 of (I); (b) aa residues 1-386,  
56-386, or  
1-211 of (II); (2) an isolated DNA comprising at least 60  
contiguous  
nucleotides (nt) of a 1552 (III) or 1296 (IV) nt NS; (3) an  
expression  
vector comprising a DNA as in (A) or (I); (4) a purified  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* polypeptide selected from: (a) a  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*  
polypeptide of (I) in mature form; (b) a \*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\*  
polypeptide of (II) in mature form; and (c) a fragment of a

polypeptides  
as in (a) or (b) which is capable of binding TRAIL; (5) a  
purified  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptide comprising an aa  
sequence that is at  
least 90% identical to aa sequence selected from: (a) aa  
residues 56-386  
of (I) or (II), and (b) residues 56-211 of (I); (6) an oligomer  
comprising  
at least 2 \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptides as in  
(5), and (7) an  
antibody that is directed against a \*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\*  
polypeptide as in (4) or an antigen-binding fragment of the  
antibody.  
USE - The \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptides  
can be used for  
binding TRAIL, e.g. to measure or inhibit the biological  
activity of  
TRAIL. The \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* polypeptides  
can be used for  
treating thrombotic microangiopathies, e.g. thrombotic  
thrombocytopenic  
purpura (TTP) or haemolytic-uremic syndrome (HUS),  
clotting of small blood  
vessels in e.g. AIDS, multiple sclerosis or systemic lupus  
erythematosus  
or for reducing TRAIL-mediated death of T cells in  
HIV-infected patients.  
They can also be used to purify TRAIL or  
TRAIL-expressing cells or as  
carriers for delivering agents to cells bearing TRAIL. The  
products can  
also be used for detection and diagnosis.  
Dwg.0/2

L2 ANSWER 28 OF 41 MEDLINE

DUPLICATE 9  
ACCESSION NUMBER: 1999248188 MEDLINE  
DOCUMENT NUMBER: 99248188 PubMed ID: 10229846  
TITLE: TRAIL (Apo-2L) and TRAIL receptors in  
human placenta:

implications for immune privilege.  
AUTHOR: Phillips T A; Ni J; Pan G; Ruben S M; Wei  
Y F; Pace J L;  
Hunt J S  
CORPORATE SOURCE: Departments of Anatomy and Cell  
Biology, Pathology and  
Laboratory Medicine, and Molecular and  
Integrative  
Physiology, University of Kansas Medical Center,  
Kansas

City, KS 66160, USA.  
CONTRACT NUMBER: HD02528 (NICHHD)  
HD24212 (NICHHD)  
HD29156 (NICHHD)

SOURCE: JOURNAL OF IMMUNOLOGY, (1999 May  
15) 162 (10) 6053-9.  
Journal code: IFB; 2985117R. ISSN: 0022-1767.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals;  
Priority Journals  
ENTRY MONTH: 199906  
ENTRY DATE: Entered STN: 19990628  
Last Updated on STN: 19990628  
Entered Medline: 19990614

AB Mechanisms accounting for protection of the fetal  
seriallograft from  
maternal immune cells remain incompletely understood. In  
other contexts,  
interactions between TRAIL (TNF-related  
apoptosis-inducing ligand/Apo-2L)  
and its receptors kill activated lymphocytes. The purpose of  
this study  
was therefore to investigate the potential of the TRAIL/  
\*\*\*TRAIL\*\*\* -  
\*\*\*R\*\*\* system to protect the placenta against immune  
cell attack.  
Analysis by Northern blotting demonstrated mRNAs  
encoding TRAIL as well as  
the four TRAIL receptors (DR4, DR5, DcR1/TRID,  
DcR2/TRUND) in human  
placentas. Immunohistochemical experiments demonstrated  
that TRAIL protein  
is prominent in syncytiotrophoblast, an uninterrupted  
placental cell layer  
that is continuously exposed to maternal blood, as well as in  
macrophage-like placental mesenchymal cells (Hofbauer  
cells). Studies on  
cell lines representing trophoblasts (Jar, JEG-3 cells) and  
macrophages  
(U937, THP-1 cells) showed that both lineages contained  
TRAIL mRNA and  
that steady state levels of transcripts were increased 2- to  
11-fold by  
IFN-gamma. By contrast, cell lineage-specific differences  
were observed in

expression of the \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* genes. Although all four lines contained mRNA encoding the apoptosis-inducing DR5 receptor, only trophoblast cells contained mRNA encoding the DeR1 decoy receptor and only macrophages contained DeR2 decoy receptor transcripts. DR4 mRNA was present only in THP-1 cells and was the only \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* transcript increased by IFN-gamma. Cytotoxicity assays revealed that the two trophoblast cell lines were resistant, whereas the two macrophage lines were partially susceptible to killing by rTRAIL. Collectively, the results are consistent with a role for the TRAIL/ \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* system in the establishment of placental immune privilege.

L2 ANSWER 29 OF 41 MEDLINE  
 DUPLICATE 10  
 ACCESSION NUMBER: 1999290669 MEDLINE  
 DOCUMENT NUMBER: 99290669 PubMed ID: 10364001  
 TITLE: Relation of TNF-related apoptosis-inducing ligand (TRAIL) receptor and FLICE-inhibitory protein expression to TRAIL-induced apoptosis of melanoma.  
 AUTHOR: Zhang X D; Franco A; Myers K; Gray C; Nguyen T; Hersey P  
 CORPORATE SOURCE: Immunology and Oncology Unit, Department of Surgical Sciences, Newcastle, NSW, Australia.  
 SOURCE: CANCER RESEARCH, (1999 Jun 1) 59 (11) 2747-53.  
 Journal code: CNF; 2984705R. ISSN: 0008-5472.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199906  
 ENTRY DATE: Entered STN: 19990714  
 Last Updated on STN: 19990714  
 Entered Medline: 19990629  
 AB Past studies have shown that apoptosis mediated by TNF-related apoptosis-inducing ligand (TRAIL) is regulated by the expression of two death receptors [TRAIL receptor 1 (TRAIL-R1) and TRAIL-R2] and two decoy receptors (TRAIL-R3 and TRAIL-R4) that inhibit apoptosis. In previous studies, we have shown that TRAIL but not other members of the tumor necrosis factor family induce apoptosis in approximately two-thirds of melanoma cell lines. Here, we examined whether the expression of \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* at the mRNA and protein level in a panel of 28 melanoma cell lines and melanocytes correlated with their sensitivity to TRAIL-induced apoptosis. We report that at least three factors appear to underlie the variability in TRAIL-induced apoptosis. (a) Four of nine cell lines that were insensitive to TRAIL-induced apoptosis failed to express death receptors, and in two instances, lines were devoid of all TRAIL-Rs. Southern analysis suggested this was due to loss of the genes for the death receptors. (b) Despite the presence of mRNA for the \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*, some of the lines failed to express \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* protein on their surface. This was evident for TRAIL-R1 and more so for the TRAIL decoy receptors TRAIL-R3 and -R4. Studies on permeabilized cells revealed that the receptors were located within the cytoplasm and redistribution from the cytoplasm may represent a posttranslational control mechanism. (c) Surface expression of TRAIL-R1 and -R2 (but not TRAIL-R3 and -R4) showed an overall correlation with TRAIL-induced apoptosis. However, certain melanoma cell lines and clones were relatively resistant to TRAIL-induced apoptosis despite the absence of decoy receptors and moderate levels of TRAIL-R1 and -R2 expression. This may indicate the presence of inhibitors within the cells, but resistance to apoptosis could not be correlated with expression of the caspase inhibitor FLICE-inhibitory protein. mRNA for another TRAIL

receptor, osteoprotegerin, was expressed in 22 of the melanoma lines but not on melanocytes. Its role in induction of apoptosis remains to be studied. These results appear to have important implications for future clinical studies on TRAIL.

L2 ANSWER 30 OF 41 MEDLINE  
 DUPLICATE 11  
 ACCESSION NUMBER: 1999323989 MEDLINE  
 DOCUMENT NUMBER: 99323989 PubMed ID: 10395688  
 TITLE: IFN-gamma mediates a novel antiviral activity through dynamic modulation of TRAIL and TRAIL receptor expression.  
 AUTHOR: Sedger L M; Shows D M; Blanton R A; Peschon J J; Goodwin R G; Cosman D; Wiley S R  
 CORPORATE SOURCE: Department of Molecular Immunology, Immunex Corporation, Seattle, WA 98101, USA. sedgerl@immunex.com  
 SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Jul 15) 163 (2) 920-6.  
 Journal code: IFB; 2985117R. ISSN: 0022-1767.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199907  
 ENTRY DATE: Entered STN: 19990806  
 Last Updated on STN: 19990806  
 Entered Medline: 19990729  
 AB TNF-related apoptosis-inducing ligand (TRAIL) is able to kill many transformed cells of diverse tissue types. We show that TRAIL is inducible by IFN-gamma, by TNF-alpha, and by infection with human CMV, and has potent antiviral activity in vitro. CMV infection and IFN-gamma also reciprocally modulate TRAIL receptor ( \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* ) expression. CMV infection increased the expression of TRAIL-R1 and -R2, whereas IFN-gamma down-regulated the expression of TRAIL-Rs on uninfected fibroblasts. Moreover, IFN-gamma significantly decreased the basal level of NF-kappaB activation, a known survival factor that inhibits apoptosis. Thus, TRAIL selectively kills virus-infected cells while leaving uninfected cells intact, and IFN-gamma potentiates these effects by dynamic modulation of TRAIL and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* expression and by sensitizing cells to apoptosis. The regulation of TRAIL and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* expression may represent a general mechanism that contributes to the control of TRAIL-mediated apoptosis.

L2 ANSWER 31 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 1999:263918 BIOSIS  
 DOCUMENT NUMBER: PREV199900263918  
 TITLE: To die or not to die-The quest of the TRAIL receptors.  
 AUTHOR(S): Degli-Esposti, Mariapia (1)  
 CORPORATE SOURCE: (1) Department of Microbiology, University of Western Australia, QEII Medical Centre, L Block, corner Hampden Rd. and Monash Ave., Nedlands, Perth, WA, 6009 Australia  
 SOURCE: Journal of Leukocyte Biology, (May, 1999) Vol. 65, No. 5, pp. 535-542. ISSN: 0741-5400.  
 DOCUMENT TYPE: General Review  
 LANGUAGE: English  
 SUMMARY LANGUAGE: English  
 AB The last 18 months have witnessed the characterization of several new members of the tumor necrosis factor (TNF) receptor family. Among these are five receptors for the cytotoxic ligand TRAIL (TNF-related apoptosis-inducing ligand). Two of these receptors, TRAIL-R1 and TRAIL-R2, contain classical cytoplasmic death domains and are able to transduce an apoptotic signal. The others lack functional death domains and are not able to promote cell death. Indeed, one of the receptors for TRAIL, osteoprotegerin (OPG) is a soluble protein whose activities

so far have been shown to be inhibition of osteoclastogenesis and increased bone density in vivo. The existence of multiple receptors for TRAIL suggests an unexpected complexity to TRAIL-mediated biological functions.

L2 ANSWER 32 OF 41 WPIDS COPYRIGHT 2001  
 DERWENT INFORMATION LTD DUPLICATE 12  
 ACCESSION NUMBER: 1998-480767 [41] WPIDS  
 DOC. NO. CPI: C1998-145392  
 TITLE: New TRAIL receptor protein and related oligomers, nucleic acid, vectors - used to inhibit TRAIL activity, e.g. in cases of thrombocytic purpura, clotting in small blood vessels etc., also for diagnosis.  
 DERWENT CLASS: B04 D16  
 INVENTOR(S): RAUCH, C; WALCZAK, H  
 PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP  
 COUNTRY COUNT: 27  
 PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG  
 WO 9835986 A1 19980820 (199841)\* EN 56  
 RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE  
 W: AU CA IL JP KR MX NO NZ  
 AU 9866505 A 19980808 (199904)  
 EP 1005488 A1 20000607 (200032) EN  
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE  
 US 6072047 A 20000606 (200033)  
 NZ 336929 A 20001124 (200065)  
 MX 9907234 A1 20000101 (200115)

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9835986	A1	WO 1998-US2239	19980211
AU 9866505	A	AU 1998-66505	19980211
EP 1005488	A1	EP 1998-908474	19980211
US 6072047	A	US 1997-799861	19970213
	CIP of	US 1997-815255	19970312
	CIP of	US 1997-829536	19970328
	CIP of	US 1997-869852	19970604
		US 1997-883036	19970626
NZ 336929	A	NZ 1998-336929	19980211
		WO 1998-US2239	19980211
MX 9907234	A1	MX 1999-7234	19990805

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9866505	A Based on	WO 9835986
EP 1005488	A1 Based on	WO 9835986
NZ 336929	A Based on	WO 9835986

PRIORITY APPLN. INFO: US 1997-883036 19970626; US 1997-799861 19970213; US 1997-815255 19970312; US 1997-829536 19970328; US 1997-869852 19970604  
 AN 1998-480767 [41] WPIDS  
 AB WO 9835986 A UPAB: 19981014  
 Purified TRAIL-receptor polypeptide ( \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* ); TRAIL = tumour necrosis factor-related apoptosis-inducing ligand) that can bind TRAIL and includes the sequence VPANEGD. Also new are:  
 (1) oligomers containing 2-4 \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* molecules;  
 (2) isolated \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* DNA (I), its fragments and DNA or RNA complements;  
 (3) expression vectors containing (I);  
 (4) host cells containing this vector, and  
 (5) antibodies (Ab) against \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*, and its antigen-binding fragments.  
 USE - \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* is used:  
 (i) to purify or inhibit activity of TRAIL, in vitro or in vivo, particularly its apoptosis-inducing action;  
 (ii) to measure amounts of TRAIL;  
 (iii) to identify TRAIL-expressing cells;  
 (iv) as carrier for therapeutic or diagnostic agents to such cells;  
 (v) as reagents for study effects of inhibiting TRAIL/ \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* interactions.  
 \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\*, or its nucleic acid, can be



Fas/Apo1-mediated activation of JNK was unaffected by the expression of GFP-DeltaFADD, suggesting that in Fas/Apo1 signaling the apoptotic pathway and the activation of JNK diverge at a level proximal to the receptor, upstream of or parallel to FADD.

L2 ANSWER 36 OF 41 MEDLINE

DUPLICATE 15

ACCESSION NUMBER: 1998211672 MEDLINE

DOCUMENT NUMBER: 98211672 PubMed ID: 9551946

TITLE: Lymphocyte inhibitor of TRAIL (TNF-related apoptosis-inducing ligand): a new receptor

protecting lymphocytes from the death ligand TRAIL.

AUTHOR: Mongkolsapaya J; Cowper A E; Xu X N; Morris G; McMichael A J; Bell J I; Screaton G R

CORPORATE SOURCE: Molecular Immunology Group, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom.

SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Jan 1) 160 (1) 3-6.

Journal code: IFB; 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals;

Priority Journals

OTHER SOURCE: GENBANK-AF033845

ENTRY MONTH: 199805

ENTRY DATE: Entered STN: 19980514

Last Updated on STN: 19980514

Entered Medline: 19980507

AB Apoptosis can be triggered by the engagement of cell surface receptors by their ligands. A growing number of receptors belonging to the TNF receptor

family have been identified that contain a conserved cytoplasmic death

domain. These include Fas, TNF-R1, lymphocyte-associated receptor of death

(LARD), DR4, and \*\*\*TNF\*\*\* - \*\*\*related\*\*\*

\*\*\*apoptosis\*\*\* -

\*\*\*inducing\*\*\* \*\*\*ligand\*\*\* \*\*\*receptor\*\*\*

inducer of cell killing-2 (TRICK2). The latter two are receptors for the cytotoxic ligand

TNF-related apoptosis-inducing ligand (TRAIL), and one of the paradoxes

raised by the cloning of these molecules was why do most cells not die

upon contact with the widely expressed TRAIL molecule?

This is a

particular problem for lymphocytes that express DR4 and TRICK2 and are in

constant circulation through TRAIL-expressing tissues. We have cloned LIT

(lymphocyte inhibitor of TRAIL), which lacks a death domain. LIT is

expressed predominantly on PBL, where it can competitively inhibit

TRAIL-induced apoptosis through DR4/TRICK2, and may function to modulate

lymphocyte sensitivity to TRAIL.

L2 ANSWER 37 OF 41 MEDLINE

DUPLICATE 16

ACCESSION NUMBER: 97431692 MEDLINE

DOCUMENT NUMBER: 97431692 PubMed ID: 9285725

TITLE: TRICK2, a new alternatively spliced receptor that

transduces the cytotoxic signal from TRAIL.

AUTHOR: Screaton G R; Mongkolsapaya J; Xu X N; Cowper A E;

McMichael A J; Bell J I

CORPORATE SOURCE: Molecular Immunology Group, Institute of Molecular Medicine

John Radcliffe Hospital Oxford, OX3 9DS, UK.

SOURCE: CURRENT BIOLOGY, (1997 Sep 1) 7 (9) 693-6.

Journal code: B44; 9107782. ISSN: 0960-9822.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AF018657;

GENBANK-AF018658

ENTRY MONTH: 199802

ENTRY DATE: Entered STN: 19980217

Last Updated on STN: 19990129

Entered Medline: 19980203

AB A subset of the tumour necrosis factor (TNF) receptor family contain a

conserved intracellular motif, the death domain.

Engagement of these

receptors by their respective ligands initiates a signalling cascade that

rapidly leads to cell death by apoptosis. We have cloned a new member of

this family, TRICK2, the TRAIL ( \*\*\*TNF\*\*\* -

\*\*\*related\*\*\*

\*\*\*apoptosis\*\*\* - \*\*\*inducing\*\*\* \*\*\*ligand\*\*\* )

\*\*\*receptor\*\*\*

inducer of cell killing 2. TRICK2 is expressed in a number of cell types,

and to particularly high levels in lymphocytes and spleen.

Two isoforms of the TRICK2 mRNA are generated by alternative pre-mRNA

splicing and differ by a 29 amino-acid extension to the extracellular domain.

Overexpression

of TRICK2 rapidly induced apoptosis in 293T cells; this induction was

dependent upon the presence of the death domain of TRICK2. Using a soluble

molecule containing the TRICK2 extracellular domain, we demonstrated that

TRICK2, like DR4 [1], is a receptor for TRAIL/APO-2L [2,3] and could

inhibit TRAIL-induced killing of lymphocyte lines, such as the Jurkat

T-cell line. TRAIL is upregulated upon lymphocyte

activation, as is the

intensively studied ligand for Fas, FasL [4]. TRAIL and its receptors

might therefore provide another system for the regulation of lymphocyte

selection and proliferation, as well as providing an additional weapon in

the armoury of cytotoxic lymphocytes.

L2 ANSWER 38 OF 41 MEDLINE

DUPLICATE 17

ACCESSION NUMBER: 97242415 MEDLINE

DOCUMENT NUMBER: 97242415 PubMed ID: 9087414

TITLE: Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis

induced by death receptors.

AUTHOR: Thorne M; Schneider P; Hofmann K; Fickenscher H; Meinel E;

Neipel F; Mattmann C; Burns K; Bodmer J L; Schroter M;

Scaffidi C; Krammer P H; Peter M E; Tschoep J

CORPORATE SOURCE: Institute of Biochemistry, University of Lausanne,

Epalinges, Switzerland.

SOURCE: NATURE, (1997 Apr 3) 386 (6624) 517-21.

Journal code: NSC; 0410462. ISSN: 0028-0836.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-U93872

ENTRY MONTH: 199704

ENTRY DATE: Entered STN: 19970507

Last Updated on STN: 20000303

Entered Medline: 19970428

AB Viruses have evolved many distinct strategies to avoid the host's

apoptotic response. Here we describe a new family of viral inhibitors

(v-FLIPs) which interfere with apoptosis signalled through death receptors

and which are present in several gamma-herpesviruses (including

Kaposi's-sarcoma-associated human herpesvirus-8), as well as in the

tumorigenic human molluscipoxvirus. v-FLIPs contain two death-effector

domains which interact with the adaptor protein FADD, and this inhibits

the recruitment and activation of the protease FLICE by the CD95 death

receptor. Cells expressing v-FLIPs are protected against apoptosis induced

by CD95 or by the related death receptors TRAMP and \*\*\*TRAIL\*\*\* -

\*\*\*R\*\*\*. The herpesvirus saimiri FLIP is detected late during the lytic

viral replication cycle, at a time when host cells are partially protected

from CD95-ligand-mediated apoptosis. Protection of virus-infected cells

against death-receptor-induced apoptosis may lead to higher virus

production and contribute to the persistence and oncogenicity of several

FLIP-encoding viruses.

L2 ANSWER 39 OF 41 SCISEARCH COPYRIGHT 2001

ISI (R)

ACCESSION NUMBER: 1998:79792 SCISEARCH

THE GENUINE ARTICLE: YR236

TITLE: Dominant-negative FADD inhibits TNFR60-,

Fas/Apo1- and

\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* /Apo2-mediated cell death but not

gene induction

AUTHOR: Wajant H (Reprint); Johannes F J; Haas E; Sieminski K;

Schwenzer R; Schubert G; Weiss T; Grell M;

Scheurich P

CORPORATE SOURCE: UNIV STUTTGART, INST CELL BIOL & IMMUNOL, ALLMANDRING 31,

D-70569 STUTTGART, GERMANY (Reprint)

COUNTRY OF AUTHOR: GERMANY

SOURCE: CURRENT BIOLOGY, (15 JAN 1997) Vol. 8, No. 2, pp. 113-116.

Publisher: CURRENT BIOLOGY LTD, 34-42

CLEVELAND STREET,

LONDON, ENGLAND W1P 6LB.

ISSN: 0960-9822.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 27

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Fas/Apo1 and other cytotoxic receptors of the tumor necrosis factor

receptor (TNFR) family contain a cytoplasmic death domain (Db) [1-11] that

activates the apoptotic process by interacting with the DD-containing

adaptor proteins TNFR-associated Db protein (TRADD) [12,13] and

pas-associated DD protein (FADD/MORT1) [14,15], leading to the activation

of cysteine proteases of the caspase family [16]. Stimulation of Fas/Apo1

reads to the formation of a receptor-bound death-inducing signaling

complex (DISC), consisting of FADD and two different forms of caspase-8.

[17-19]. Transient expression of a dominant-negative mutant of FADD

impairs TNFR60-mediated and Fas/Apo1-mediated apoptosis [13,20], but has

no effect on TNF-related apoptosis-inducing ligand (TRAIL/Apo2L)-induced

cell death [7-10,21]. To study the function of FADD in DD-receptor

signaling in more detail, we established HeLa cells that stably expressed

a green fluorescent protein (GFP)-tagged dominant-negative mutant of FADD,

GFP-Delta FADD. Interestingly, expression of this mutant inhibited cell

death induced by TNFR60, Fas/Apo1 and \*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* /Apo2. In

addition, GFP-Delta FADD did not interfere with TNF-mediated gene

induction or with activation of NF-kappa B or Jun N-terminal kinase (JNK),

demonstrating that FADD is part of the TNFR60-initiated apoptotic pathway

but does not play a role in TNFR60-mediated gene induction.

Fas/Apo1-mediated activation of JNK was unaffected by the expression of

GFP-Delta FADD, suggesting that in Fas/Apo1 signaling the apoptotic

pathway and the activation of JNK diverge at a level proximal to the

receptor, upstream of or parallel to FADD.

L2 ANSWER 40 OF 41 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1988:70537 BIOSIS

DOCUMENT NUMBER: BA85:36836

TITLE: MEASUREMENT OF THE GRISTLE

CONTENT IN BEEF BY MACROSCOPIC

UV FLUOROMETRY.

AUTHOR(S): SWATLAND H J

CORPORATE SOURCE: DEP. FOOD SCI., UNIV.

GUELPH, GUELPH, ONTARIO, CAN.

SOURCE: J ANIM SCI, (1987) 65 (1), 158-164.

CODEN: JANSAG. ISSN: 0021-8812.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB Ultraviolet light (365 nm) was directed at an angle of 45 degree, onto

meat samples in a circular aperture (3 cm diameter). Fluorescence

emissions were measured with a monochromator and a photomultiplier tube.

Intact tendons and elastic ligaments had a strong fluorescence emission

peak around 440 to 450 nm and only weak fluorescence around 510 nm.

Tissues such as lean meat and adipose tissue that contain a matrix of

reticular fibers (Type III collagen) had very low fluorescence around 440

to 450 nm so that their peak emittance was the weak fluorescence peak at

510 nm. The 510/440 nm ratio of fluorescence emissions was measured in



used to  
treat conditions involving defective or inadequate  
\*\*\*TRAIL\*\*\*  
\*\*\*R\*\*\*, e.g. thrombotic thrombocytopenic purpura,  
haemolytic-uraemic  
syndrome, clotting of small blood vessels, systemic lupus  
erythematosus  
and TRAIL-mediated apoptosis of T cells in human immune  
deficiency virus  
infections.  
Ab are used for detection or purification of  
\*\*\*TRAIL\*\*\*  
\*\*\*R\*\*\*, and to inhibit TRAIL/ \*\*\*TRAIL\*\*\*  
\*\*\*R\*\*\* interaction,  
i.e. to treat the above diseases; also agonist antibodies can  
be used to  
induce apoptosis in some cancer or virus-infected cells.  
(1) can be used to detect abnormal \*\*\*TRAIL\*\*\*  
\*\*\*R\*\*\* genes  
and as antisense therapeutics.  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* may be administered in  
soluble form or it  
is immobilised on a solid support and used for  
extracorporeal treatment of  
blood.  
Dwg.0/3

L2 ANSWER 33 OF 41 WPIDS COPYRIGHT 2001  
DERWENT INFORMATION LTD  
ACCESSION NUMBER: 1998-399141 [34] WPIDS  
CROSS REFERENCE: 1998-399142 [34]  
DOC. NO. CPI: C1998-120982  
TITLE: Human TRAIL receptor without an  
intracellular domain  
polypeptide - used in the diagnosis of immune  
system-related disorder(s).  
DERWENT CLASS: B04 D16  
INVENTOR(S): EBNER, R; FENG, P; GENTZ, R L; NI,  
J; RUBEN, S M; WEI, Y;  
YU, G  
PATENT ASSIGNEE(S): (HUMA-N) HUMAN GENOME  
SCI INC  
COUNTRY COUNT: 82  
PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG  
WO 9830693 A2 19980716 (199834)\* EN 91  
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE  
IT KE LS LU MC MW NL OA  
PT SD SE SZ UG ZW  
W: AL AM AU AZ BA BB BG BR BY CA CH CN  
CU CZ DE DK EE ES FI GB GE  
GH GM GU HW ID IL IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI  
SK SL TJ TM TR TT UA UG  
US UZ VN YU ZW  
AU 9862386 A 19980803 (199850)  
EP 990031 A2 20000405 (200021) EN  
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC  
NL PT SE  
CN 1247567 A 20000315 (200031)  
JP 2001505060 W 20010417 (200128) 150

#### APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9830693	A2	WO 1998-US152	19980113
AU 9862386	A	AU 1998-62386	19980113
EP 990031	A2	EP 1998-904528	19980113
		WO 1998-US152	19980113
CN 1247567	A	CN 1998-801836	19980113
JP 2001505060	W	JP 1998-531036	19980113
		WO 1998-US152	19980113

#### FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9862386	A Based on	WO 9830693
EP 990031	A2 Based on	WO 9830693
JP 2001505060	W Based on	WO 9830693

PRIORITY APPLN. INFO: US 1997-54885 19970807; US  
1997-35496 19970114

AN 1998-399141 [34] WPIDS  
CR 1998-399142 [34]  
AB WO 9830693 A UPAB: 20010522

Isolated nucleic acid molecule (I) comprises a sequence at  
least 95 %  
identical to: (a) a nucleotide sequence encoding a mature or  
immature TRID  
(TRAIL ( \*\*\*TNF\*\*\* - \*\*\*related\*\*\*  
\*\*\*apoptosis\*\*\*  
\*\*\*inducing\*\*\* - \*\*\*ligand\*\*\* ) \*\*\*receptor\*\*\*  
without an  
intracellular domain) polypeptide having a 259 amino acid

(aa) sequence  
(A) (includes 26 aa signal peptide) given in the specification  
or the  
mature or immature TRID polypeptide encoded by ATCC  
97798; (b) a  
nucleotide sequence encoding the soluble extracellular  
domain of a TRID  
polypeptide comprising aa 27-240 of (A) or the soluble  
extracellular  
domain of the TRID polypeptide encoded by ATCC 97798;  
and (c) a nucleotide  
sequence complementary to any of the nucleotide  
sequences of (a) and (b).  
Also claimed are: (1) an isolated nucleic acid comprising  
a  
nucleotide sequence at least 95 % identical to a sequence  
encoding  
residues m-233, 1-x or m-x of the 259 aa sequence; m= -1 to  
27 and x=  
123-233; (2) an isolated nucleic acid comprising a nucleotide  
sequence at  
least 95% identical to: (a) a sequence encoding the TRID  
protein encoded  
by ATCC 97798 having an N-terminal truncation of 1-52 aa;  
and/or (b) a  
sequence encoding the TRID protein encoded by ATCC  
97798 having a  
C-terminal truncation of 1-110 aa; (3) an isolated nucleic  
acid comprising  
a polynucleotide which encodes an epitope bearing portion  
of a TRID  
polypeptide encoded by (1); (4) a recombinant vector  
containing (1); (5) a  
recombinant host cell comprising the vector of (4); (6) a  
TRID polypeptide  
(A) encoded by (1); and (7) an antibody that binds  
specifically to (A).  
USE - TRID is a member of the tumour necrosis factor  
receptor (TNFR)  
family also known as TNFR-5. TRID is expressed in  
haematopoietic tissues  
and other normal human tissues. For a number of immune  
system-related  
disorders, substantially altered (whether increased or  
decreased) levels  
of TRID gene expression can be detected, therefore the  
TRID polypeptides,  
nucleic acids and antibodies are useful in the diagnosis of  
such immune  
system related disorders. Mutations of the TRID gene can  
also be detected.  
TRID can also be used to identify ligands which may be  
useful in the  
treatment of apoptosis related disorders. TRID is  
administered to humans  
at a parenteral dose of 0.01 to 1 mg/kg/day.  
Dwg.0/10

L2 ANSWER 34 OF 41 MEDLINE  
DUPLICATE 13  
ACCESSION NUMBER: 1998414313 MEDLINE  
DOCUMENT NUMBER: 98414313 PubMed ID: 9743381  
TITLE: TNFR80-dependent enhancement of  
TNFR60-induced cell death  
is mediated by TNFR-associated factor 2 and is  
specific for  
TNFR60.  
AUTHOR: Weiss T; Grell M; Sieminski K;  
Muhlenbeck F; Durkop H;  
Pfizenmaier K; Scheurich P; Wajant H  
CORPORATE SOURCE: Institute of Cell Biology and  
Immunology, University of  
Stuttgart, Germany.  
SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Sep  
15) 161 (6) 3136-42.  
Journal code: IFB; 2985117R. ISSN: 0022-1767.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals;  
Priority Journals  
ENTRY MONTH: 199810  
ENTRY DATE: Entered STN: 19981020  
Last Updated on STN: 19981020  
Entered Medline: 19981006  
AB Costimulation of TNFR80 can strongly enhance  
TNFR60-induced cell death. In  
this study, we show that this enhancement is TNFR60  
selective, as neither  
TNF-related apoptosis-inducing ligand/Apo2 ligand-,  
Apo1/Fas-, ceramide-,  
nor daunorubicin-mediated cell death was affected by  
costimulation of  
TNFR80. We further demonstrate that TNFR-associated  
factor 2 (TRAF2) is  
critically involved in both negative and positive regulation of  
TNF-induced cell death. Overexpression of TRAF2 and of a  
TRAF2 mutant,  
deficient in nuclear factor-kappaB activation, selectively  
desensitized

and enhanced, respectively, TNFR60-induced cell death in  
HeLa cells.  
However, upon costimulation of TNFR80, which mediates  
activation of  
nuclear factor-kappaB and the c-Jun amino-terminal kinase  
via TRAF2,  
TNF-induced cell death is drastically enhanced in parental  
and  
TRAF2-transfected, but not in TRAF2 (87-501)-transfected  
cells. These data  
point to a critical role of TRAF2 in the apoptotic TNFR  
cross talk,  
whereby the TNFR80-dependent enhancement of  
TNFR60-induced cell death is  
due to TNFR80-mediated negative regulation of TRAF2  
function(s). An  
interference with TRAF2 function was confirmed  
independently by analysis  
of c-Jun amino-terminal kinase activation via TNFR60 upon  
prestimulation  
of TNFR80. We propose that the apoptotic TNFR cross talk  
is based on  
TNFR80-mediated abrogation of antiapoptotic  
TRAF2-dependent signaling  
pathways initiated by TNFR60, but not Apo1/Fas or the  
apoptotic  
\*\*\*TNF\*\*\* - \*\*\*related\*\*\* - \*\*\*apoptosis\*\*\*  
\*\*\*inducing\*\*\*  
\*\*\*ligand\*\*\* - \*\*\*receptors\*\*\*

L2 ANSWER 35 OF 41 MEDLINE  
DUPLICATE 14  
ACCESSION NUMBER: 1998089174 MEDLINE  
DOCUMENT NUMBER: 98089174 PubMed ID: 9427646  
TITLE: Dominant-negative FADD inhibits TNFR60-,  
Fas/Apo1- and  
\*\*\*TRAIL\*\*\* - \*\*\*R\*\*\* /Apo2-mediated cell  
death but not  
gene induction.  
AUTHOR: Wajant H; Joharanes F J; Haas E; Sieminski  
K; Schwenzer R;  
Schubert G; Weiss T; Grell M; Scheurich P  
CORPORATE SOURCE: Institute of Cell Biology and  
Immunology, University of  
Stuttgart, Alldrandring 31, 70569 Stuttgart,  
Germany..  
harald.wajant@po.uni-stuttgart.de  
SOURCE: CURRENT BIOLOGY, (1998 Jan 15) 8 (2)  
113-6.  
Journal code: B44; 9107782. ISSN: 0960-9822.  
PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199803  
ENTRY DATE: Entered STN: 19980326  
Last Updated on STN: 19980326  
Entered Medline: 19980318  
AB Fas/Apo1 and other cytotoxic receptors of the tumor  
necrosis factor  
receptor (TNFR) family contain a cytoplasmic death domain  
(DD) [1] [2] [3]  
[4] [5] [6] [7] [8] [9] [10] [11] that activates the apoptotic  
process by  
interacting with the DD-containing adaptor proteins  
TNFR-associated DD  
protein (TRADD) [12] [13] and Fas-associated DD protein  
(FADD/MORT1) [14]  
[15], leading to the activation of cysteine proteases of the  
caspase  
family [16]. Stimulation of Fas/Apo1 leads to the formation  
of a  
receptor-bound death-inducing signaling complex (DISC),  
consisting of FADD  
and two different forms of caspase-8 [17] [18] [19].  
Transient expression  
of a dominant-negative mutant of FADD impairs  
TNFR60-mediated and  
Fas/Apo1-mediated apoptosis [13] [20], but has no effect on  
TNF-related  
apoptosis-inducing ligand (TRAIL/Apo2L)-induced cell  
death [7] [8] [9]  
[10] [21]. To study the function of FADD in DD-receptor  
signaling in more  
detail, we established HeLa cells that stably expressed a  
green  
fluorescent protein (GFP)-tagged dominant-negative mutant  
of FADD,  
GFP-DeltaFADD. Interestingly, expression of this mutant  
inhibited cell  
death induced by TNFR60, Fas/Apo1 and \*\*\*TRAIL\*\*\*  
- \*\*\*R\*\*\* /Apo2. In  
addition, GFP-DeltaFADD did not interfere with  
TNF-mediated gene induction  
or with activation of NF-kappaB or Jun N-terminal kinase  
(JNK),  
demonstrating that FADD is part of the TNFR60-initiated  
apoptotic pathway  
but does not play a role in TNFR60-mediated gene  
induction.

comminuted meat samples containing varying mixtures of lean meat and gristle and varying mixtures of muscles with a high and low gristle content. The 510/440 nm ratio was correlated with the ratio of lean meat/gristle ( $r = .96$ ,  $P < .005$ ). The 510/440 nm ratio was correlated with the ratio of longissimus/shank meat (two \*\*\*trails\*\*\*;  $r = .93$ ,  $P < .01$ ; and  $r = .94$ ,  $P < .005$ ). Results were only slightly changed when samples had dry surfaces or when samples were mixed with adipose particles. The relationship between the area of gristle in the samples and the 510/440 nm ratio was curvilinear with the greatest sensitivity to the fewest gristle fragments.

L2 ANSWER 41 OF 41 WPIDS COPYRIGHT 2001  
DERWENT INFORMATION LTD  
ACCESSION NUMBER: 1974-17418V [39] WPIDS  
TITLE: Hydraulic brake system for \*\*\*trail\*\*\*  
\*\*\*\*

has distributor valv responsive to mechanical  
brake of towing vehicle.

DERWENT CLASS: Q18  
PATENT ASSIGNEE(S): (BOSC) BOSCH GMBH ROBERT  
COUNTRY COUNT: 4  
PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG

US 3836205 A 19740917 (197439)\*  
GB 1379373 A 19750102 (197501)  
AT 7304222 A 19760715 (197632)  
DE 2225357 B 19810326 (198114)

PRIORITY APPLN. INFO: DE 1972-2225357 19720525  
\*\*\*\* DATA NOT AVAILABLE FOR THIS ACCESSION  
NUMBER